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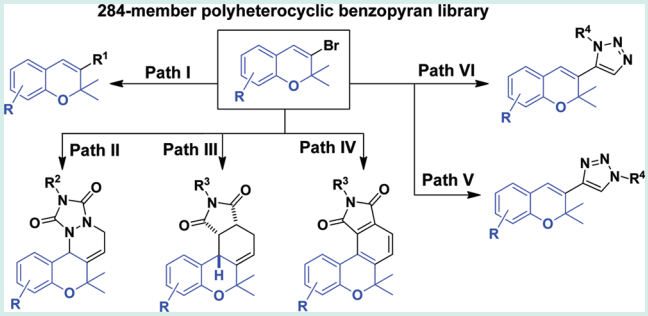
# Construction of Polyheterocyclic Benzopyran Library with Diverse Core Skeletons through Diversity-Oriented Synthesis Pathway: Part II

Mingyan Zhu,[†] Byung Joon Lim,[†] Minseob Koh,[†] and Seung Bum Park*[,†,‡]

[†]Department of Chemistry and [‡]Department of Biophysics and Chemical Biology, Seoul National University, Seoul 151−747, Korea

Supporting Information

**ABSTRACT:** As a continuation of our previous report (*J. Comb. Chem.* **2010**, *12*, 548−558), we accomplished the diversity-oriented synthesis of polyheterocyclic small-molecule library with privileged benzopyran substructure. To ensure the synthetic efficiency, we utilized the solid-phase parallel platform and the fluorous-tag-based solution-phase parallel platform to construct a 284-member polyheterocyclic library with six distinct core skeletons with an average purity of 87% on a scale of 5−10 mg. This library was designed to maximize the skeletal diversity with discrete core skeletons in three-dimensional space and the combinatorial diversity with four different benzopyranyl starting materials and various building blocks. Together with our reported benzopyranyl library, we completed the construction of polyheterocyclic benzopyran library with 11 unique scaffolds and their molecular diversity was visualized in chemical space using principle component analysis (PCA).




**KEYWORDS:** *benzopyran, parallel synthesis, fluorous tag, diversity-oriented synthesis, skeletal diversity*

## INTRODUCTION

The systematic perturbation of gene products with small-molecule modulators has been one of the major research areas in the interdisciplinary research field of chemical biology as well as pharmaceutical industry.[1] The development of high throughput screening technology toward increasing number of disease targets led to the ever-increasing demand for the collection of novel drug-like small molecules with maximized molecular diversity.[2] To accomplish this, synthetic communities adopted a diversity-oriented synthesis (DOS) approach that aims for the efficient generation of complex and diverse compound libraries containing a large number of structurally diversified molecular frameworks.[3] We have been particularly interested in the development of divergent and robust synthetic pathways for the systematic construction of a library of drug-like small molecules via the creative reconstruction of polyheterocycles embedded with privileged substructures including benzopyran, benzodiazepine, pyrazole, pyrazolopyrimidine, tetrahydroindazolone, and so on; we named this approach a privileged-substructure-based diversity-oriented synthesis (pDOS).[4] Noteworthy, our novel molecular frameworks with privileged substructure showed the enhanced selectivity and relevancy toward multiple biological assay systems as small-molecule modulators for specific biological targets.[5]

To construct novel molecular frameworks using pDOS strategy, we aimed to develop a practical synthetic route for unique polyheterocycles containing a benzopyranyl substructure, which is a well-known privileged structural motif observed in many biologically active natural products and therapeutic agents.[6−8] We previously reported a concise and efficient DOS pathway for the construction of eleven core skeletons via various chemical transformations.[9a] On the basis of our initial report, we also demonstrated the practical construction of 434-member library containing five core skeletons using solid-phase parallel synthesis format.[9b] Herein, we carried out the construction of six discrete core skeletons embedded with the benzopyranyl substructure as a continuation of our previous efforts.

As shown in Figure 1, our divergent synthetic route was designed to access six discrete core skeletons from key benzopyranyl intermediates **3**{*1*−*4*} through a series of chemical transformations, such as palladium-mediated Suzuki coupling (Path I), Suzuki coupling-based vinylation followed by aza Diels−Alder reaction (Path II) and Diels−Alder reaction (Path III), and subsequent aromatization of Diels−Alder adducts (Path IV), and Stille coupling-based alkynylation followed by copper(I)- and ruthenium(II)-catalyzed regioselective alkyne−azide cycloaddition to produce 1,4-disubstituted triazoles (Path V) and 1,5-disubstituted triazoles (Path VI), respectively. Paths II, III, and IV allow the construction of benzopyranyl tetracycles (**8**, **9**, and **10**) with three unique trajectories of core skeletons in 3-dimensional space. Paths V and VI can generate the regioisomeric pairs of 1,4- and 1,5-disubstituted heterobiaryl skeletons (**12** and **13**) with different orientations of appendence. These synthetic paths were designed to maximize the molecular diversity of resulting small-molecule library. To ensure the efficiency in library construction without laborious

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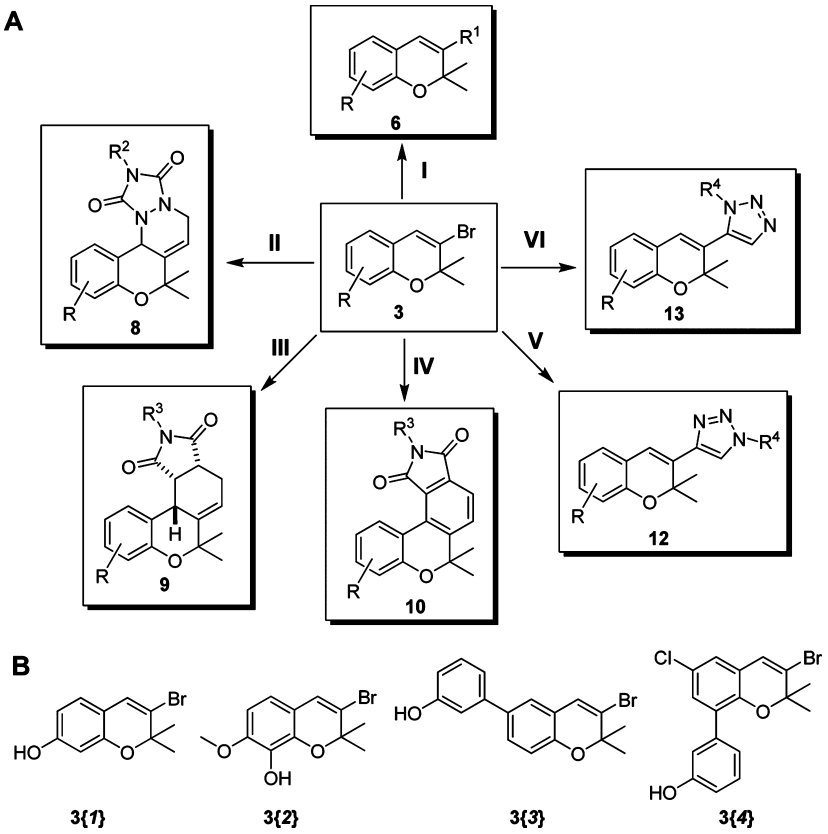



**Figure 1.** (A) Divergent pDOS strategy for the construction of six discrete core skeletons embedded with benzopyran substructure: Suzuki coupling [Path I]; vinylation, subsequent Diels–Alder reaction with aza dienophile and carbon dienophile, and aromatization reaction [Paths II to IV]; alkynylation and subsequent copper(I) and ruthenium(II)-catalyzed alkyne–azide cycloaddition [Paths V and VI]. (B) Chemical structures of key benzopyranyl intermediates **3**{*1*–*4*}.

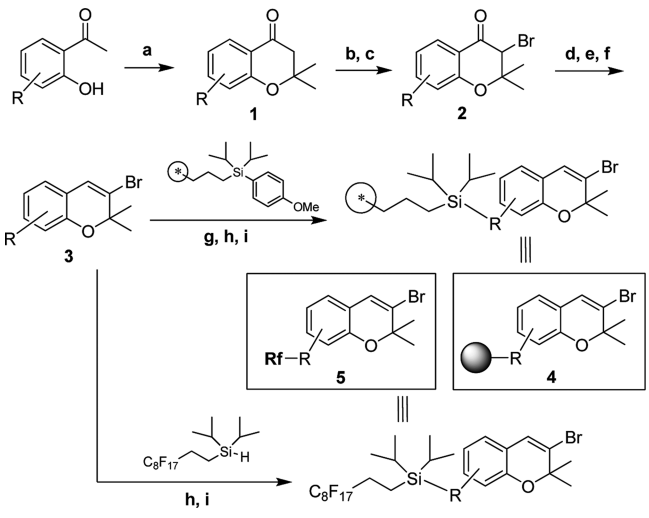
purification steps, we optimized these synthetic routes in solid-phase parallel synthesis format using polystyrene resin (Path I) and the fluorous-tag-based solution-phase parallel synthesis format (Paths II–VI). In fact, the fluorous technology has received attention from synthetic community, especially for high-throughput synthesis, because this technology retains the advantage of solution-phase reaction without the sacrifice of its synthetic throughput, due to the simple purification by fluorous-tag-based solid-phase extraction (F-SPE).[10]

## RESULTS AND DISCUSSION

We initiated the library construction with four different chromanones (**1**{*1*}–**1**{*4*}) via pyrrolidine-catalyzed cyclization of substituted *ortho*-hydroxyacetophenones with acetone (See Scheme 1). To enhance the molecular diversity and biocompatibility of final drug-like polyheterocycles, two of the chromenones, **1**{*3*} and **1**{*4*}, were prepared with an additional Suzuki coupling with 3-hydroxyphenylboronic acid to introduce biphenyl moiety, another privileged substructural motif. Four resulting chromanones **1**{*1*–*4*} were subjected to $\alpha$-bromination and subsequent silyl protection at phenolic hydroxyl group. $\alpha$-Bromoketones **2**{*1*–*4*} were reduced to $\alpha$-bromoalcohols by $NaBH_4$, followed by acid-catalyzed dehydration and subsequent silyl deprotection, to yield four vinyl bromides containing benzopyranyl substructure, **3**{*1*–*4*}, as key intermediates.

As stated earlier, our synthetic routes were adapted to solid-phase parallel synthesis and the fluorous-tag-based solution-phase parallel synthesis platform for the efficient library con-

**Scheme 1. Synthetic Scheme for Vinyl Bromide Intermediates 3[a] and their Modification on Solid Support 4 and with Fluorous Tag 5**




[a]Reagents and conditions: (a) Acetone, pyrrolidine, EtOH, reflux; for **1**{*3*–*4*}, an additional Suzuki coupling with bromo-substituted chromanone and 3-hydroxyphenylboronic acid, $Na_2CO_3$, $Pd(PPh_3)_4$, EtOH/toluene/$H_2O$, 70 °C; (b) $CuBr_2$, EtOAc/$CHCl_3$/MeOH, reflux; (c) Triisopropylsilyl chloride, imidazole, DCM, rt; (d) $NaBH_4$, EtOH, 40 °C; (e) *p*-TsOH, toluene, 80 °C; (f) TBAF, THF, rt; (g) TMSCl, DCM; (h) TfOH, DCM; (i) 2,6-Lutidine, DCM.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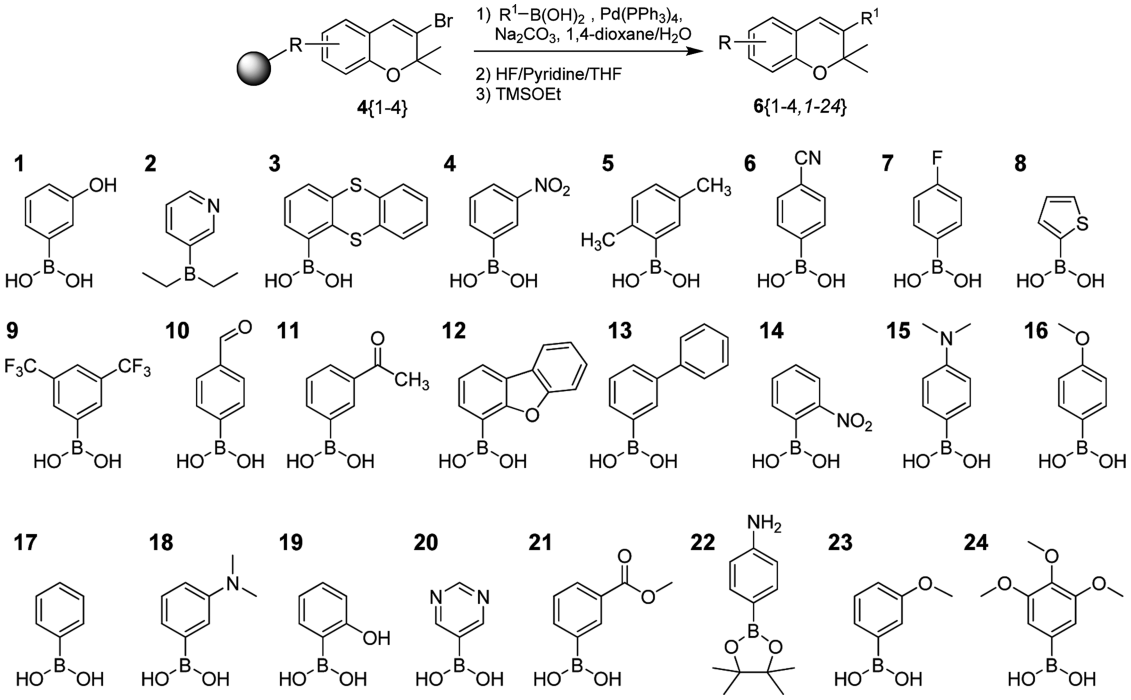
**Scheme 2. Solid-Phase Suzuki Coupling Reaction with Aryl/Heteroaryl-Boronic Acids for the Synthesis of Compounds 6{*1−4,1−24*} in Path I and the Chemical Structures of Aryl- and Heteroaryl-Boronic Acids**




struction. In the case of path I, the desired heterobiaryl compounds **6** were successfully prepared by our reported Suzuki coupling condition using vinyl bromide intermediates on solid support, **4**{*1−4*}, without any further optimizations. However, we observed incomplete reaction, even with prolonged reaction time and observed side products during the translation into solid-phase reaction in other synthetic paths (II−VI), which led us to carry them out in solution-phase with fluorous-tagged intermediates **5**{*1−4*}. After the activation of (4-methoxyphenyl)-diisopropylsilylpropyl polystyrene resin with TfOH, vinyl bromide intermediates **3**{*1−4*} were immobilized on the activated resin in the presence of 2,6-lutidine to afford polymer-bound intermediates **4**{*1−4*} (see Scheme 1). The average loading level was about 1.0 mmol/g (see Supporting Information), which was quantified by the weight gain of loaded resins and confirmed with the weight of cleaved products from loaded resins. For the preparation of vinyl bromide intermediates with fluorous tag, diisopropyl-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)silane tag was activated with TfOH and subsequently incubated with vinyl bromide intermediates **3**{*1−4*} in the presence of 2,6-lutidine to afford perfluorooctanesilyl-labeled hydroxylchromenylbromide intermediates **5**{*1−4*}.

**Solid-Phase Suzuki Reaction (Path I) to Synthesize Heterobiaryl Benzopyrans 6 {1—4, 1—24}.** The vinyl bromide moiety embedded in benzopyranyl core skeleton **3** is a good substrate for palladium-mediated C−C cross-coupling reaction. Therefore, we successfully introduced various aryl and heteroaryl moieties via Suzuki coupling of aryl/heteroaryl boronic acids with $Pd(PPh_3)_4$ and $Na_2CO_3$ in aqueous 1,4-dioxane (10% $H_2O$). As shown in Scheme 2, vinyl bromide intermediates on polymer support **4**{*1−4*} were subjected to the parallel synthesis in 96-deep well format for Suzuki-based transformation with 24 commercially available aryl- and heteroaryl-boronic acids to yield the desired heterobiaryl benzopyrans **6** in high yields and purity. These building blocks were selected to ensure the purity of final products without any loss of molecular diversity. In the case of 2,6-disubstituted arylboronic acids, we observed some side products, mainly generated by debromination of **3**, probably due to the steric demands of nearby dimethyl group to vinyl bromide intermediates. The residual palladium (or palladium black formed during the reaction) was removed by washing polymer resins with sodium diethyldithiocarbamate (0.2 M) in THF. After the standard cleavage protocol of silyl linkers using HF/pyridine and subsequent quenching with TMSOEt, the identification and purity of desired heterobiaryl benzopyrans **6**{*1−4,1−24*} were determined using LC/MS or $^1$H NMR without any further purifications. As shown in Table 1, the presence of all desired compounds was unambiguously confirmed by their molecular mass and the resulting 96-member small-molecule collection was prepared in a scale of 5−10 mg with the average purity of 86%.

**Synthesis of Benzopyranotetracycles 8{*1−4,1−12*}, 9{*3−4,1−12*}, and 10{*1−2,1−12*} through Paths II−IV.** In paths II to IV, the benzopyran-embedded dienes, the key intermediates, were obtained through the palladium-mediated vinylation to vinyl bromide intermediate **3**. In our earlier trial on solid support, we experienced the incompletion of reaction even with prolonged reaction time and observed side products, mainly the debromination of intermediate **3**. In addition, we previously used palladium-mediated Stille reaction employing tributyl(vinyl) stannane reagent for vinylation, but we tried to avoid the tin reagent due to its toxic nature and the potential contamination to final products. Therefore, we optimized the palladium-mediated Suzuki reaction with vinyl bromide intermediate with fluorous tag **5**{*1−4*} in solution-phase parallel synthesis to yield dienes **7**{*1−4*} with moderate to good yields (70−90%, see Supporting Information). For path II, the resulting dienes with fluorous tag **7**{*1−4*} were subjected to Diels−Alder reaction with various dienophiles. Through the building block screening process, we selected 12 triazolinedione-type


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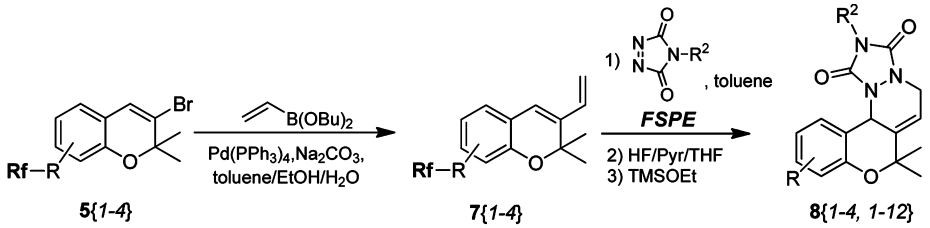
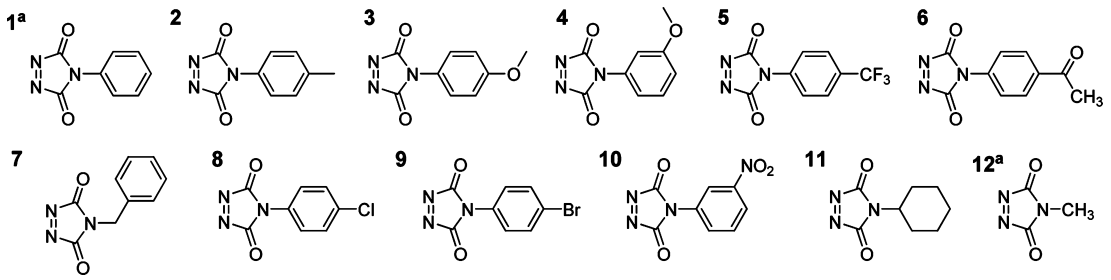
Table 1. Purities[a] of Heterobiaryl Benzopyrans 6{*1−4,1−24*} in Path I

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6{*1*,$R^1$} | 85 | 81 | 88 | 92 | 82 | 90 | 83 | 74 | 87 | 93 | 84 | 93 |
| 6{*2*,$R^1$} | 97 | 88 | 92 | 95 | 77 | 94 | 85 | 77 | 94 | 91 | 89 | 94 |
| 6{*3*,$R^1$} | 87 | 80 | 83 | 87 | 73 | 89 | 84 | 82 | 87 | 93 | 94 | 79 |
| 6{*4*,$R^1$} | 87 | 65 | 81 | 82 | 68 | 81 | 89 | 91 | 95 | 93 | 91 | 87 |
| | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** |
| 6{*1*,$R^1$} | 95 | 77 | 86 | 83 | 83 | 82 | 95 | 93 | 96 | 97 | 91 | 97 |
| 6{*2*,$R^1$} | 92 | 92 | 97 | 78 | 82 | 79 | 97 | 99 | 96 | 99 | 83 | 82 |
| 6{*3*,$R^1$} | 75 | 81 | 74 | 77 | 71 | 70 | 87 | 75 | 81 | 90 | 73 | 78 |
| 6{*4*,$R^1$} | 81 | 87 | 85 | 80 | 80 | 88 | 99 | 77 | 90 | 91 | 79 | 88 |

[a]Purities (%) were obtained by PDA-based LC/MS analysis of final compounds after cleavage from solid-support.

Scheme 3. Fluorous-Tag-Based Parallel Synthesis of 8{*1−4,1−12*} in Path II [Suzuki-Based Vinylation and Aza Diels−Alder Reaction] and the Chemical Structures of 4-Substituted-1,2,4-triazoline-3,5-diones as Building Blocks[a]




[a]Commercially available. Other triazolinediones were in-house synthesized from their precursors, 4-substituted 1,2,4-triazolidine-3,5-diones, by IBD-based in situ oxidation.[11]

azadienophiles (Scheme 3) and 12 maleimide-type carbodienophiles (Scheme 4) to ensure high yield and purity of final library members without the significant loss of their molecular diversity. In the case of azadienophiles, there is a limited commercial availability because of their instability, therefore we in-house prepared the most of 4-substituted-1,2,4-triazoline-3,5-diones as highly reactive azadienophiles via IBD-based in situ oxidation of 4-substituted-1,2,4-triazolidine-3,5-diones at room temperature. The incubation of diene intermediates 7{*1−4*} with azadienophiles provided the desired hetero-Diels−Alder tetracyclic adducts with fluorous tag, which can be readily purified by simple solid-phase extraction with fluorous cartridge (F-SPE). After removal of fluorous tag, the desired benzopyranotetracycles 8{*1−4,1−12*} were obtained with over 90% of average purity in 5−10 mg scale (Table 2).

In path III, the diene intermediate with fluorous tag 7{*1−4*} were subjected to Diels−Alder reaction with N-substituted maleimides in the presence of $ZnCl_2$ as a Lewis acid catalyst and smoothly formed endo-selective Diels−Alder products 14{*1−4,1−12*}. However, we observed the spontaneous aromatization during the removal of fluorous tag, especially in the case of 9{*1−2,1−12*} due to their inherent instability, but not in the case of 9{*3−4,1−12*}. Therefore, we converted 14{*1−2,1−12*} to the aromatized Diels−Alder adducts 15{*1−2,1−12*} by DDQ-assisted oxidative aromatization, which we classified as path IV. After the removal of fluorous tag by HF/pyridine and subsequent quenching with TMSOEt, we obtained Diels−Alder tetracyclic products 9{*3−4,1−12*} (Path III) and aromatized Diels−Alder product 10{*1−2,1−12*} (Path IV) with two unique polyheterocyclic core skeletons containing privileged benzopyran substructure. The final products in Table 2 and 3 were synthesized in a scale of 5−10 mg with over 90% of average purity, measured by LC/MS analysis of the crude products after F-SPE without any further purification. It is worth mentioning that three resulting tetracyclic core skeletons **8**, **9**, and **10** from paths II−IV contain the privileged benzopyranyl substructure, but they have unique trajectory of their core skeletons in three-dimensional space, especially the junction [N($sp^3$), C($sp^3$), and C($sp^2$), respectively] of dienophiles in Diels−Alder adducts. Furthermore, the crystal structure of hetero-Diels−Alder adduct **8** is clearly different from Diels−Alder adduct **9** because of the ring distortion and steric repulsion of lone pair electrons on nitrogen atoms in **8**, which can be clearly visualized in the aligned structures of three core skeletons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**Scheme 4. Solution-Phase Parallel Synthesis of 9{*3−4,1−12*} and 10{*1−2,1−12*} Synthesized in Path III [Suzuki-Based Vinylation and Diels−Alder reaction] and Path IV [Subsequent DDQ-Assisted Oxidative Aromatization], and the Chemical Structures of N-Substituted Maleimides as Building Blocks**

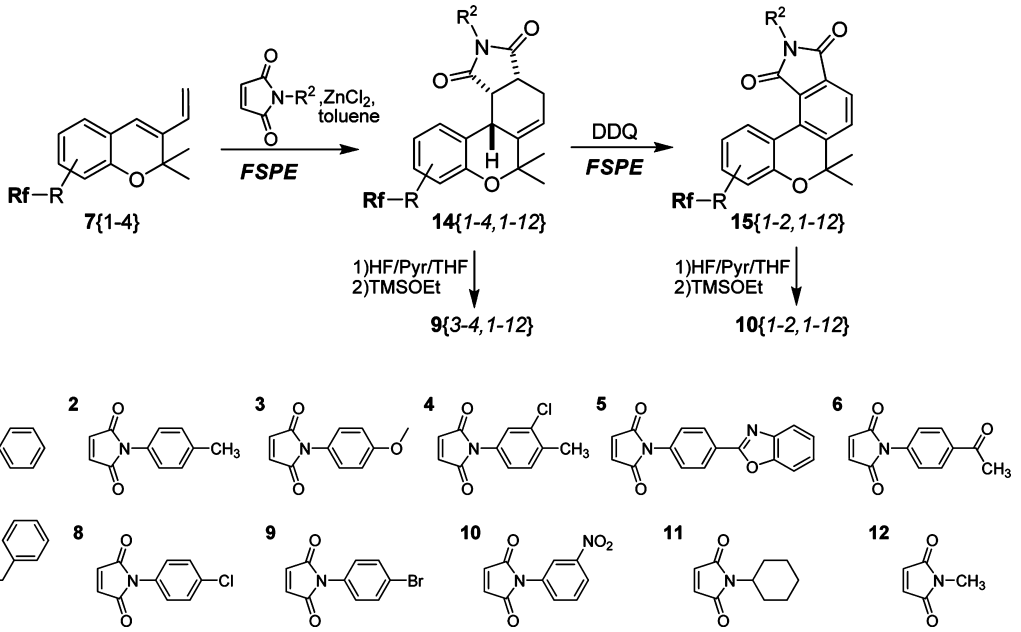





**Table 2. Purities[a] of Final Products 8{*1−4,1−12*} in Path II**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8{*1*,$R^2$} | 95 | 96 | 87 | 88 | 91 | 98 | 79 | 95 | 81 | 83 | 97 | 86 |
| 8{*2*,$R^2$} | 97 | 73 | 88 | 90 | 80 | 95 | 85 | 88 | 80 | 96 | 99 | 87 |
| 8{*3*,$R^2$} | 97 | 99 | 96 | 99 | 97 | 99 | 96 | 99 | 98 | 98 | 90 | 89 |
| 8{*4*,$R^2$} | 94 | 83 | 94 | 89 | 99 | 77 | 90 | 92 | 91 | 66 | 98 | 99 |

[a]Purities (%) were obtained by PDA-based LC/MS analysis of final compounds after F-SPE.

**Table 3. Purities[a] of Final Products 9{*3−4,1−12*} and 10{*1−2,1−12*} in Paths III and IV**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 9{*3*,$R^3$} | 92 | 98 | 96 | 92 | 94 | 95 | 92 | 93 | 87 | 96 | 92 | 76 |
| 9{*4*,$R^3$} | 90 | 86 | 97 | 92 | 93 | 88 | 89 | 81 | 72 | 85 | 89 | 90 |
| 10{*1*,$R^3$} | 80 | 92 | 97 | 93 | 94 | 99 | 80 | 85 | 87 | 99 | 99 | 95 |
| 10{*2*,$R^3$} | 99 | 97 | 96 | 96 | 77 | 94 | 93 | 96 | 93 | 99 | 86 | 94 |

[a]Purities (%) were obtained by PDA-based LC/MS analysis of final compounds after F-SPE.

(see Supporting Information Figure S2). The representative final products (**6**, **8**, **9**, and **10**) were fully characterized and analyzed in Table 4 and the Supporting Information.

**Synthesis of Benzopyranyl Triazoles 12{*1−4,1−15*} and 13{*1−4,1−8*} through Paths V and VI.** For paths V and VI, we introduced terminal alkyne to the fluorous-tagged vinyl bromide intermediates **5**{*1−4*} through palladium-mediated Stille cross-coupling reaction. Along with the ensured regiochemical control of resulting triazole analogs, we used the fluorous-tag-assisted solution-phase parallel synthesis, which allows the effective removal of toxic tin reagent, ethynyltributylstannane, compared to solid-phase synthesis. After the alkynylation of vinyl bromide intermediate with fluorous tag **5**{*1−4*}, the resulting alkynyl benzopyrans **11**{*1−4*} were subjected to copper(I)-catalyzed 1,3-dipolar cycloaddition, namely Click reaction,[12,13] with alkyl- and arylazides[14] to afford benzopyranyl triazoles. We optimized this regioselective transformation using $BrCu(PPh_3)_3$, a soluble Cu-catalyst in organic solvent, and DIPEA at 40 °C to yield benzopyranyl 1,4-disubstituted-1,2,3-triazoles **12** after removal of fluorous tag. Through the building block screening process, nine alkylazides and six arylazides were selected for the synthesis of a 60-member collection of 1,4-substituted-1,2,3-triazole-containing benzopyrans **12**{*1−4,1−15*}. The average purity, measured by LC/MS analysis of crude products, was 87% and the purities of individual final compounds are shown in Table 5.

To enhance the molecular diversity of final products with minimum structural perturbation of alkyne intermediates and azide building blocks, we performed the regioisomeric and systematic synthesis of 1,5-disubstituted-1,2,3-triazole analogs with identical substrates and building blocks. In fact, 1,5-disubstituted-1,2,3-triazole has an important implication in biological system as a mimic of cis-peptide bond.[15] In path VI, we designed the 1,5-substutited-1,2,3-triazoles as regioisomeric counterparts of "Click" products from path V. Under this objective, we selected the ruthenium(II)-catalyzed alkyne−azide cycloaddition (RuAAC) for the regioselective formation


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**Table 4. Purity and Mass Confirmation of Representative Compounds in Paths I–IV**

| ID | R | $R^{1-3}$ | Yield[a] (%) | Purity[b] (%) | MS (calcd) | MS[c] (found) |
|---|---|---|---|---|---|---|
| **6**{*1,23*} | 7-hydroxy | 3-methoxyphenyl | 58 | 91 | 283.13 | 283.07 |
| **6**{*2,15*} | 8-hydroxy-7-methoxy | 4-dimethylaminophenyl | 59 | 97 | 326.17 | 326.21 |
| **6**{*3,11*} | 6-(3-hydroxyphenyl) | 3-acetylphenyl | 53 | 94 | 371.16 | 370.96 |
| **6**{*4,19*} | 6-chloro-8-(3-hydroxyphenyl) | 2-hydroxyphenyl | 61 | >99 | 377.10 | 377.05 |
| **8**{*1,4*} | 7-hydroxy | 3-methoxyphenyl | 77 | 88 | 408.42 | 408.17 |
| **8**{*2,10*} | 8-hydroxy-7-methoxy | 3-nitrophenyl | 51 | 96 | 453.13 | 453.15 |
| **8**{*3,7*} | 6-(3-hydroxyphenyl) | Benzyl | 72 | 96 | 468.18 | 468.22 |
| **8**{*4,3*} | 6-chloro-8-(3-hydroxyphenyl) | 4-methoxyphenyl | 70 | 94 | 518.14 | 518.23 |
| **9**{*3,1*} | 6-(3-hydroxyphenyl) | phenyl | 69 | 92 | 452.18 | 452.29 |
| **9**{*4,3*} | 6-chloro-8-(3-hydroxyphenyl) | 4-methoxyphenyl | 85 | 97 | 516.15 | 516.29 |
| **10**{*1,12*} | 7-hydroxy | methyl | 59 | 95 | 308.10 | 308.10 |
| **10**{*2,1*} | 8-hydroxy-7-methoxy | phenyl | 75 | >99 | 402.13 | 402.17 |

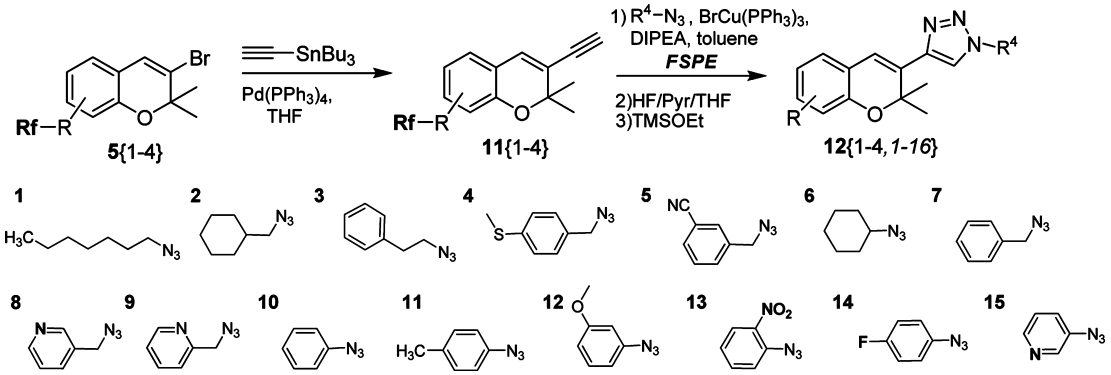
[a]Yields were calculated by the weight of final compounds obtained after cleavage from solid-support or after removal of fluorous tag and F-SPE. Yields for compounds **6** were two-step yields from **4**{*1–4*}, yields for compounds **8–10** were two- or three-step yields from **7**{*1–4*}. [b]Purities were obtained by PDA-based LC/MS analysis of final compounds. [c]Mass analysis were performed by electron spray ionization (ESI) method.

**Table 5. Purities[a] of Final Products 12{*1–4,1–15*} in Path V**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **12**{*1,R*[4]} | 85 | 84 | 88 | 93 | 92 | 87 | 90 | 76 | 93 | 86 | 81 | 82 | 82 | 82 | 90 |
| **12**{*2,R*[4]} | 77 | 80 | 83 | 95 | 86 | 93 | 86 | 81 | 87 | 94 | 81 | 86 | 81 | 89 | 73 |
| **12**{*3,R*[4]} | 75 | 85 | 84 | 80 | 81 | 75 | 76 | 73 | 87 | 75 | 85 | 92 | 81 | 80 | 90 |
| **12**{*4,R*[4]} | 90 | 97 | 95 | 99 | 96 | 96 | 81 | 96 | 97 | 95 | 96 | 95 | 91 | 95 | 99 |

[a]Purities (%) were obtained by PDA-based LC/MS analysis of final compounds after F-SPE.

**Scheme 5. Stille-Coupling-Based Alkynylation and Cu(I)-Catalyzed Alkyne-Azide Cycloaddition (CuAAC) in Path V and the Chemical Structures of Alkyl- and Arylazides as Building Blocks**




of 1,5-disubstituted-1,2,3-triazoles[16] and optimized RuAAC in solution-phase parallel reaction with fluorous-tagged alkynyl benzopyran intermediates **11**{*1–4*}. Unlike copper(I)-catalyzed alkyne–azide cycloaddition (CuAAC), we observed the low conversion of arylazide in RuAAC condition, therefore we did not use aryl azides as building blocks for path VI. As shown in Scheme 6, 32-member collection of 1,5-substituted-1,2,3-triazole-containing benzopyrans **13**{*1–4,1–8*} was successfully constructed through the modification of reported RuAAC procedures from **11**{*1–4*} and eight azide building blocks after the removal of fluorous tag. The identification and purity of final products **13**{*1–4,1–8*} was confirmed by LC-MS and their average purity was over 83%. The representative final products (**12** and **13**) were fully characterized and analyzed in Table 6 and Supporting Information.

**Completion of Benzopyran library with 11 Unique Core Skeletons.** In this study, we constructed a 284-member pilot library with six unique core skeletons embedded with benzopyran substructure via the DOS-based synthetic exercise of paths I–VI. We previously reported the construction of 434-member polyheterocycle library as the first generation of benzopyran library with five discrete synthetic paths. As shown in Figure 2, we synthesized over 700 compounds with 11 unique core skeletons embedded with benzopyran substructure.

For the systematic analysis of molecular diversity, we carried out principal component analysis (PCA) of the whole members of polyheterocyclic benzopyran library using 14 representative molecular descriptors (including molecular weight, number of rotatable bonds, ALogP, topological polar surface area, hydrophobic surface area, etc. See Supporting Information for detail). As shown in Figure 3, individual compounds of 718-member benzopyran library are widely spread in the chemical space with large molecular diversity. The 284-member collection containing six core skeletons of this study is labeled in black square (part B in Figure 2) and the 434-member collection containing five core skeletons of previously reported benzopyran library[8b]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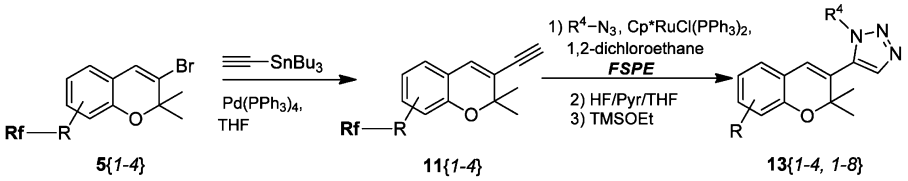
**Scheme 6. Ru(II)-Catalyzed Alkyne-Azide Cycloaddition and Purities of Final Products 13{*1−4,1−8*}[a]**




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| **13**{*1,R*$^4$} | 91 | 95 | 87 | 95 | 90 | 87 | 69 | 92 |
| **13**{*2,R*$^4$} | 72 | 93 | 78 | 81 | 79 | 74 | 74 | 79 |
| **13**{*3,R*$^4$} | 79 | 79 | 73 | 70 | 74 | 74 | 82 | 67 |
| **13**{*4,R*$^4$} | 91 | 93 | 90 | 85 | 90 | 91 | 82 | 80 |

[a]Purities (%) were obtained by PDA-based LC/MS analysis of final compounds after F-SPE.

**Table 6. Purity and Mass Identification of Representative Compounds 12{*1−4,1−15*} and 13{*1−4,1−8*} in Paths V and VI**

| ID | R | R$^4$ | yield[a] (%) | purity[b] (%) | MS (calcd) | MS[c] (found) |
|---|---|---|---|---|---|---|
| **12**{*1,1*} | 7-hydroxy | *n*-heptyl | 72 | 85 | 342.21 | 341.97 |
| **12**{*1,15*} | 7-hydroxy | 3-pyridyl | 82 | 90 | 321.13 | 321.17 |
| **12**{*2,4*} | 8-hydroxy-7-methoxy | 4-methylthiobenzyl | 68 | 95 | 410.14 | 410.24 |
| **12**{*3,2*} | 6-(3-hydroxyphenyl) | cyclohexylmethyl | 81 | 85 | 416.23 | 416.33 |
| **12**{*4,3*} | 6-chloro-8-(3-hydroxyphenyl) | 2-phenylethyl | 73 | 95 | 458.16 | 458.13 |
| **13**{*1,1*} | 7-hydroxy | n-heptyl | 66 | 91 | 342.21 | 342.27 |
| **13**{*2,4*} | 8-hydroxy-7-methoxy | 4-methylthiobenzyl | 82 | 81 | 410.15 | 410.16 |
| **13**{*3,3*} | 6-(3-hydroxyphenyl) | 2-phenylethyl | 77 | 73 | 424.19 | 424.33 |
| **13**{*4,3*} | 6-chloro-8-(3-hydroxyphenyl) | 2-phenylethyl | 70 | 90 | 458.16 | 458.22 |

[a]Yields were calculated by the weight of final compounds obtained after removal of fluorous tag and F-SPE, as two-step yields from **11**{*1−4*}. [b]Purities were obtained by PDA-based LC/MS analysis of final compounds. [c]Mass analysis were performed by electron spray ionization (ESI) method.

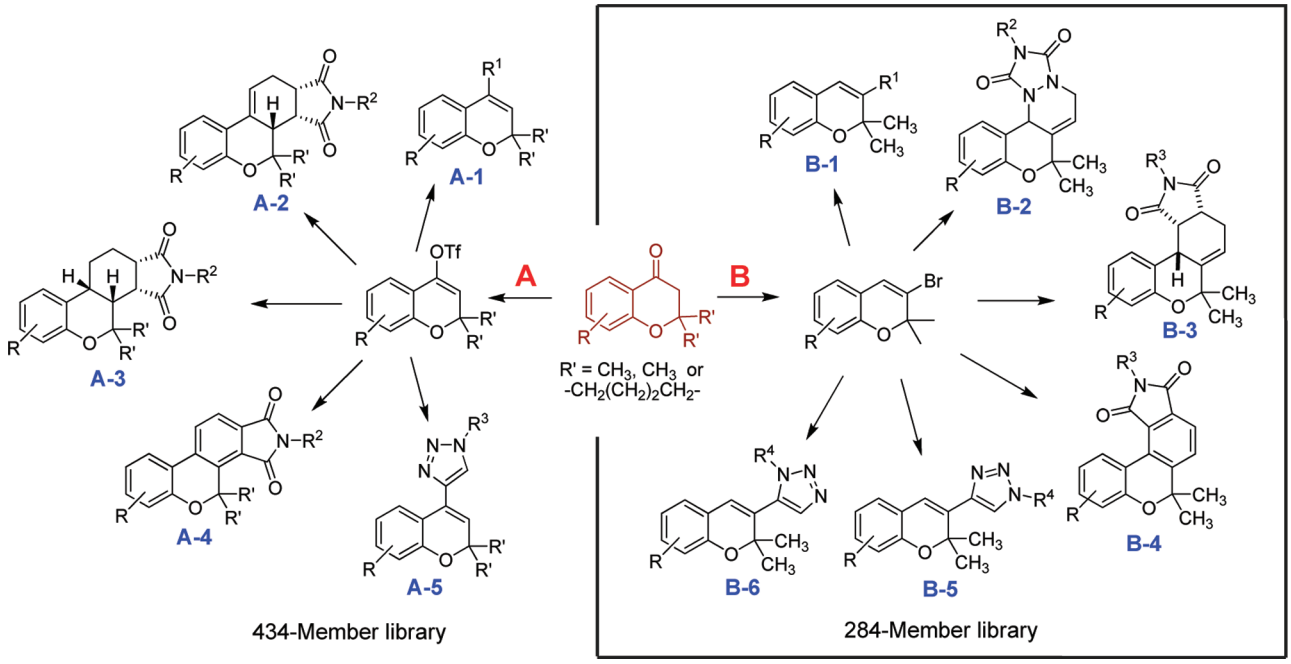



**Figure 2.** Overall schematic representation of benzopyran library using diversity-oriented synthesis strategy (Paths A and B).

is labeled in gray triangle (part A in Figure 2); this analysis clearly visualizes that the DOS-based construction of diverse core skeletons can be effective to maximize the molecular diversity of drug-like compound library. In addition, a PCA analysis of 284-member library constructed in this study shows that the different paths (I−VI) allow to access the different chemical space via the wide distribution of compounds upon changes of core skeletons and appendices (see Supporting Information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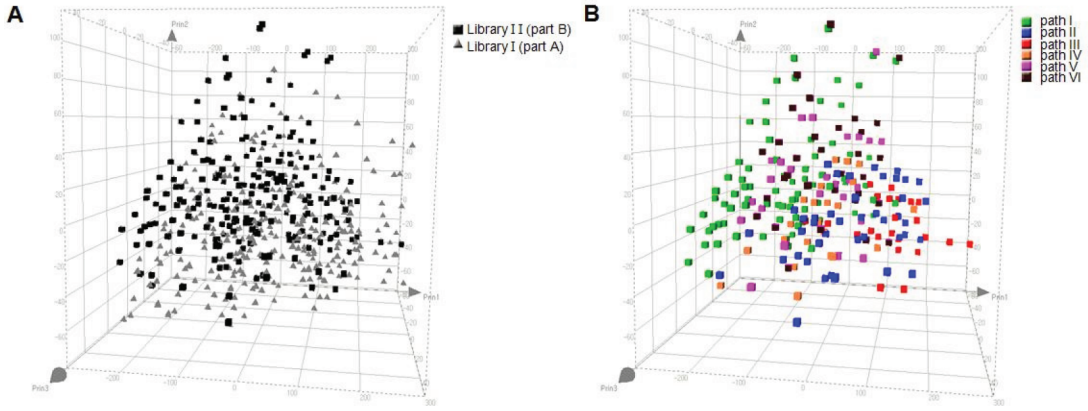


**Figure 3.** Principle component analysis (PCA) of the total in-house synthetized benzopyran library. (A) PCA of the 434-member library labeled in gray triangle (Path A) and 284-member library labeled in black square (Path B); (B) Color coding of 6 unique core skeletons of path B to visualize their influence on the molecular diversity of 284-member library. Green, **6**{*1*−*4*,*1*−*24*}; blue, **8**{*1*−*4*,*1*−*12*}; red, **9**{*3*−*4*,*1*−*12*}; orange, **10**{*1*−*2*,*1*−*12*}; pink, **12**{*1*−*4*,*1*−*15*}; brown, **13**{*1*−*4*,*1*−*8*}.

Figure S1). Therefore, we are confident that the development of novel DOS pathway and subsequent construction of drug-like compound collections with diverse core skeletons, especially embedded with privileged substructure (i.e., benzopyran in this study), can play a pivotal roles for the expansion of molecular diversity in chemical biology study and drug discovery.

## CONCLUSION

In conclusion, we accomplished the construction of small-molecule library with six discrete core skeletons embedded with privileged benzopyran substructure using DOS strategy. The practical synthesis was achieved through the versatile application of solid-phase parallel synthesis and fluorous-tag-based solution-phase parallel synthesis. The skeletal diversity of resulting polyheterocycles was efficiently achieved through the various chemical transformations of vinyl bromide intermediates **3**{*1*−*4*}, such as palladium-mediated Suzuki reaction for arylation (Path I), Suzuki-based vinylation and subsequent aza Diels−Alder reaction (Path II), Diels−Alder reaction (Path III), and aromatization (Path IV), Stille-based alkynylation and subsequent copper(I)- and ruthenium(II)-catalyzed alkyne−azide cycloaddition (Paths V and VI) to yield a 284-member library with six discrete core skeletons, **6**{*1*−*4*,*1*−*24*}, **8**{*1*−*4*,*1*−*12*}, **9**{*3*−*4*,*1*−*12*}, **10**{*1*−*2*,*1*−*12*}, **12**{*1*−*4*,*1*−*15*}, and **13**{*1*−*4*,*1*−*8*}, respectively. The excellent *endo*-selectivity of Diels−Alder reaction yields diastereo-chemically enriched polyheterocycle **9**{*3*−*4*,*1*−*12*}, and aza-Diels−Alder reaction yields conformationally unique polyheterocycle **8**{*1*−*4*,*1*−*12*}. The metal-catalyzed regioselective synthesis of triazoles also allows the construction of two regioisomeric benzopyran-containing core skeletons with identical building blocks. The second generation of benzopyran library was constructed with 284 compounds in a scale of 5−10 mg with over 87% of average purity. In conjunction of our first generation of benzopyran library, we constructed total 718-member polyheterocycle library containing 11 unique core skeletons embedded with privileged benzopyran substructure. Extensive biological evaluations of this benzopyran library are current underway, which will lead to the identification of small-molecule modulators and potential therapeutic agents.

## EXPERIMENTAL SECTION

**General Loading Procedure of Compound 3 on Solid Support.** (4-Methoxyphenyl)-diisopropylsilylpropyl polystyrene resins (1.5 mmol/g, 1.0 equiv) were swelled for 15 min in $CH_2Cl_2$ with TMSCl (4.0 equiv.) to remove residual moisture trapped in solid supports. After filtration and washing with $CH_2Cl_2$, the resins were treated with 3% (v/v) trifluoromethanesulfonic acid (6.0 equiv) in $CH_2Cl_2$ for 15 min. Then, the resins were filtered, washed three times with $CH_2Cl_2$, and suspended in $CH_2Cl_2$. The activated resins were incubated with compound **3** (3.0 equiv) in the presence of 2,6-lutidine (8.0 equiv) at room temperature for 12 h. After filtration, the resulting resins were washed three times each with $CH_2Cl_2$ and THF and dried in vacuo to afford polymer-bound vinyl bromide benzopyranyl intermediates **4**{*1*−*4*}.

**General Procedure for the Attachment of Fluorous Tag to Compound 3.** To a solution of diisopropyl-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)silane (1.0 equiv) in anhydrous $CH_2Cl_2$, trifluoromethanesulfonic acid (1.3 equiv) was added at 0 °C, and the mixture was stirred at room temperature for 15 h. Then, a solution of compound **3** (1.3 equiv) and 2,6-lutidine (2.6 equiv) in anhydrous $CH_2Cl_2$ was added and stirred at room temperature for additional 2 h. The reaction mixture was quenched with aqueous $NH_4Cl$ and extracted with $CH_2Cl_2$ and ether. The combined organic extracts were dried over anhydrous $MgSO_4$(s), filtered, and concentrated in vacuo. The resulting mixture was purified with silica-gel flash column chromatography to provide the vinyl bromide benzopyranyl intermediates with fluorous tag **5**{*1*−*4*}.

**General Purification Procedure of Fluorous-tagged Compounds by F-SPE.** The reaction mixture was dissolved in minimum amount of DMF and loaded onto a FluorFlash@-F-SPE cartridge preconditioned with MeOH/$H_2O$ (80:20). The cartridge was eluted with 80:20 MeOH/H2O for the non-fluorous fraction, followed by about same amount of MeOH for the fluorous fraction. The positive pressure was given to elute samples. The fractions were concentrated in GeneVac vacuum centrifuge. The cartridge was washed thoroughly with acetone and eluted with MeOH/$H_2O$ (80/20, v/v) for reusage.

**General Procedure for Solid-Phase Suzuki Coupling for the Synthesis of Compound Set 6 (Path I).** Vinyl bromide intermediates on solid supports **4**{*1*−*4*} were charged into each well of a 96-deep-well filtration block (~25 mg/well;


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see Supporting Information) and solutions of 24 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), $Na_2CO_3$ (5.0 equiv) in $H_2O$/1,4-dioxane (10% v/v) was added to each well of the reaction block. The reaction mixture was shaken at 70 °C in a rotating oven for 24 h, followed by washing with THF, $CH_2Cl_2$, DMF, and MeOH (three times each). The palladium catalyst was removed by swelling the resin three times, each time for 1 h, with a metal-chelating solution (sodium diethyldithiocarbamate 0.2 M in THF), and washed with THF and $CH_2Cl_2$. 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 excess HF (HF/pyridine protocol). After removing resins by filtration, the filtrate was condensed in vacuo using a GeneVac vacuum centrifuge to obtain the desired products **6**{*1−4,1−24*}.

**General Procedure of Suzuki-Based Vinylation for the Synthesis of Diene Intermediate 7.** To a solution of fluorous-tagged vinyl bromide intermediates **5**{*1−4*} (1.0 equiv) and vinylboronic acid dibutyl ester (1.2 equiv.) in a mixed solvent of toluene/EtOH/water (1:1:1), $Pd(PPh_3)_4$ (0.03 equiv) and $Na_2CO_3$ (2.5 equiv) was added. The reaction vessel was purged with argon and the reaction mixture was stirred at 70 °C for 12 to 18 h. After the completion of reaction monitored by TLC, the reaction was stopped and diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$(s), filtered, and condensed under reduced pressure. The resulting mixture was purified by silica-gel flash column chromatography to provide the desired diene intermediates **7**{*1−4*} for the subsequent aza- and carbon-Diels−Alder reaction.

**General Procedure of Aza Diels−Alder Reaction (Path II).** Compounds **7**{*1−4*} (∼0.05 mmol each; see Supporting Information) were dissolved in toluene (0.5 mL) and divided into individual reaction vials, where 4-substituted-1,2,4-triazoline-3,5-dione (0.06 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature for 30 min. The 4-substituted-1,2,4-triazoline-3,5-diones used in path II were in-house prepared through the *in situ* oxidation of its precursor, 4-substituted-1,2,4-triazolidine-3,5-dione (1.2 equiv.) with iodobenzene diacetate (IBD, 1.2 equiv.) for 20 min at ambient temperature in THF. The reaction completion of 1,2,4-triazoline-3,5-dione formation was indicated by the color changes of reaction solution (from clear to red or violet). After the reaction completion monitored by TLC, the reaction mixture was condensed in vacuo using a GeneVac vacuum centrifuge. The resulting residue was redissolved in DMF (0.5 mL) and purified by F-SPE to provide aza Diels−Alder adducts **8**{*1−4, 1−12*}.

**General Procedure of Diels−Alder Reaction and Aromatization (Paths III and IV).** Compounds **7**{*1−4*} (∼0.05 mmol each; see Supporting Informaion) in toluene (0.5 mL) were divided in individual reaction vials, where N-substituted maleimide (0.1 mmol, 2.0 equiv) and $ZnCl_2$ (0.01 mmol, 0.2 equiv.) was added. The mixture was heated to 70 °C for 12 to 24 h. After the completion of reaction monitored by TLC, the reaction mixture was condensed in vacuo using a GeneVac vacuum centrifuge. The residue was redissolved in DMF (0.5 mL) and purified by F-SPE to provide fluorous-tagged product **14**{*1−4,1−12*}. For aromatization, Diels−Alder products **14**{*1−2,1−12*} was dissolved in toluene and treated with 2,3-dichloro-5,6-dicyanao-1,4-benzoquinone (DDQ) (2.0 equiv) for 20 min at ambient temperature. After the completion of reaction monitored by TLC, the reaction mixture was condensed in vacuo using a GeneVac vacuum centrifuge. Purification by F-SPE provided the aromatization product **15**{*1−2,1−12*} with fluorous tag.

**General Procedure of Stille-Based Alkynylation for the Synthesis of Intermediate 11.** To a solution of compounds **5**{*1−4*} in anhydrous THF, $Pd(PPh_3)_4$ (0.05 equiv.) and ethynyltributylstannane (2.0 equiv.) was added. The reaction mixture was purged with argon and heated to 60 °C for 5 to 8 h. After the completion of reaction monitored by TLC, the reaction mixture was quenched with brine and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$(s), filtered, and condensed under reduced pressure. The residue was purified by silica-gel flash column chromatography to provide alkynyl benzopyran intermediates **11**{*1−4*} for the subsequent cycloaddition with azide building blocks.

**General Procedure of Copper(I)-Catalyzed Alkyne−Azide Cycloaddition (Path V).** To compounds **11**{*1−4*} (∼0.05 mmol each; see Supporting Information) divided in individual reaction vials, a solution of azide (0.1 mmol, 2.0 equiv), $BrCu(PPh_3)_3$ (0.005 mmol, 0.1 equiv), and diisopropylethylamine (0.06 mmol, 1.2 equiv) in toluene (0.5 mL) was added. The reaction mixture was heated to 40 °C for 5 h. After reaction completion monitored by TLC, the reaction mixture was condensed in vacuo using a GeneVac vacuum centrifuge, resuspended in DMF (0.5 mL), and purified by F-SPE to provide benzopyranyl 1,4-disubstituted-1,2,3-triazoles **12**{*1−4,1−15*} with fluorous tag.

**General Procedure of Ruthenium(II)-Catalyzed Alkyne−Azide Cycloaddition (Path VI).** To compounds **11**{*1−4*} (∼0.05 mmol each; see Supporting Information) divided in individual reaction vials, a solution of azide (0.125 mmol, 2.5 equiv.) and $Cp^*RuCl(PPh_3)_2$ (0.005 mmol, 0.1 equiv.) in 1,2-dichloroethane (0.5 mL) was added. The reaction mixture was purged with argon and heated to 80 °C for 4 h. After reaction completion monitored by TLC, the reaction mixture was condensed in vacuo using a GeneVac vacuum centrifuge, resuspended in DMF (0.5 mL), and purified by F-SPE to provide benzopyranyl 1,5-disubstituted-1,2,3-triazoles **13**{*1−4,1−8*} with fluorous tag.

**General Procedure for the Removal of Fluorous Tag and Purification of Final Product with F-SPE.** Fluorous tag was removed by treating fluorous-tagged final products with HF/pyridine/THF (5/5/90) solution (1.0 mL) for 2 h at ambient temperature, followed by the addition of TMSOEt (1.0 mL) to quench excess HF (HF/pyridine protocol). The resulting mixture was condensed in vacuo using a GeneVac vacuum centrifuge. The residue was redissolved in DMF (0.3 mL) and purified by F-SPE. The desired untagged product was collected in the MeOH/$H_2O$ fraction, which was condensed in vacuo using a Genevac vacuum centrifuge. After the lyophilization of cleaved product in acetonitrile/water (1/1, v/v), the final products was obtained in powder and analyzed by LC/MS and $^1H$ NMR.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Detailed synthetic procedures, full characterization and $^1H/^{13}C$, 2D NMR spectra of representative compounds, LC/MS analysis and principal component analysis of all library members, X-ray crystal structure and 3-D structure alignment of representative compounds **8**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.


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## AUTHOR INFORMATION


### Corresponding Author

*E-mail: sbpark@snu.ac.kr.



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