Efficient Parallel Synthesis of Privileged Benzopyranylpyrazoles via Regioselective Condensation of β-Keto Aldehydes with Hydrazines

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In this study, the practical construction of a pilot library with benzopyranylpyrazole, a novel core skeleton synthesized through the recombination of privileged structures, benzopyran and pyrazole, was successfully conducted through the efficient utilization of solution-phase parallel synthesis using solid-phase reagents and solid-phase parallel synthesis. We have also developed a novel procedure for the synthesis of benzopyranylpyrazoles via regioselective condensation of substituted hydrazines with β-keto aldehydes. The diversity of this core skeleton was expanded by the regioselective introduction of alkyl- and aryl-substituents at the R^1 diversity point on the pyrazole moiety and by the introduction of piperazine on the benzopyran substructure, which provide the R^2 diversity point. Lastly, the introduction of a nitro group on the benzopyran moiety was found to accelerate the nucleophilic aromatic substitution of piperazine and provide the R^3 diversity point at the aniline moiety through the reduction of the nitro group. In this pilot library, we only focused on the diversification at the R^1 position with either the R^2 or R^3 position, and thus maximized the diversity through the rational selection of building blocks using chemoinformatics. Overall, a 192-member benzopyranylpyrazole pilot library was constructed with an appending potential for further diversification. The average purity of the library is 87%.

Introduction

The specific perturbation of complex biological events with small molecules has been in the spotlight in various research disciplines, especially chemical biology and chemical genomics, due to their potential applications as therapeutic agents and research tools in biology.[1] Collections of small organic molecules became essential elements in chemical biology, and the identification of small-molecule perturbagens for biological process can pave a new road toward the unraveling of complex biological events.[2] Therefore, combinatorial chemistry has transformed into a valuable approach for the construction of novel core skeletons with high efficiency. Diversity-oriented synthesis (DOS) has been proven to be an essential tool to populate the chemical space with skeletally and stereochemically diverse small molecules with high appending potentials through complexity-generating reactions.[3] And in particular, the identification and reconstruction of privileged substructural motifs—the idea that there exist preferred molecular scaffolds that can provide ligands for diverse receptors, first introduced by Evans and co-workers in 1988—can provide unique opportunities to tap into the new biological space with novel core skeletons.[4]

We recently reported the construction of four novel core skeletons through a creative recombination of the privileged substructures: benzopyran, pyridine, pyrazole, pyrazolopyrimidine, and pyrimidine.[5] The regioselective synthesis of each heterocycle was achieved through a divergent synthetic approach from s-*cis*-enone intermediates. During our endeavor to access these novel core skeletons for DOS pathway development,[6] we gained a mechanistic understanding of the regioselective formation of arylpyrazole through the condensation of a β-keto aldehyde with arylhydrazine under various reaction conditions. In fact, the benzopyran and pyrazole motifs have been recognized because of their various biological activities. As shown in Figure 1, the pyrazole motif demonstrates diverse biological activities in parts of the B-Raf inhibitor,[7] CARM1 inhibitor,[8] CB1 receptor antagonist,[9] and EP1 receptor antagonist.[10] The benzopyran motif has also been observed in many bioactive natural products and pharmaceutical agents.[11] Therefore, we were strongly encouraged to pursue the realization of a focused library that is based on the fusion of two privileged substructures, benzopyran, and pyrazole.

Results and Discussion

Synthesis of Benzopyranylpyrazole Scaffolds 5{*1*}−5{*8*}. Even with the extensive studies on the biological activities of pyrazole derivatives, the synthesis of the pyrazole moiety has been suffered for its poor regioselectivity, especially in the case of the condensation reaction between 1,3-diketones and asymmetrically substituted hydrazines. It was recently reported that the regioselective syntheses of aryl- and alkyl-substituted pyrazoles can be achieved through the solvent effect[12] or by adjusting the activity of 1,3-diketones.[13] However, these methods are not sufficiently robust to be applied to the synthesis of various pyrazole derivatives, especially alkyl-substituted pyrazoles. We recently established the efficient synthesis of aryl-substituted benzopyranylpyrazoles through the introduction of hydroxy-substituted

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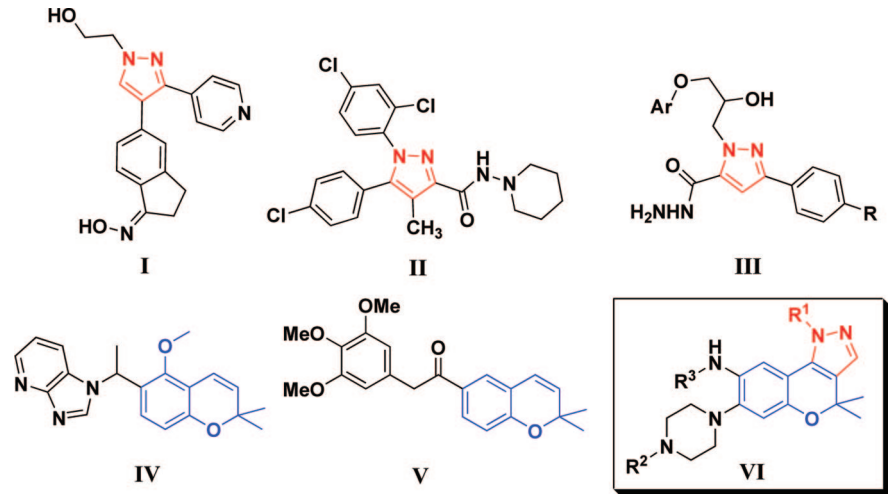
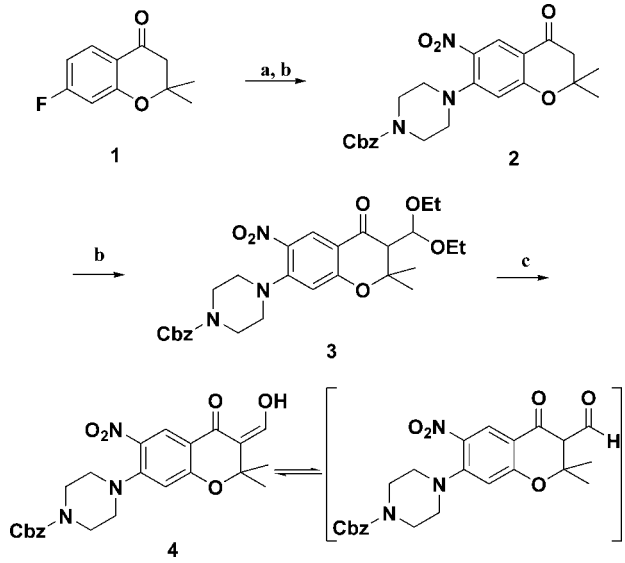


Figure 1. Bioactive molecules containing pyrazole and a benzopyran moiety: I, B-Raf inhibitor; II, CB-1 receptor antagonist; III, anticancer; IV, HIF-1 inhibitor; V, NADH inhibitor; VI, our designed heterocycle.

Scheme 1. Synthesis of Hydroxy-Substituted *S-cis*-enone as a Key Intermediate[a]



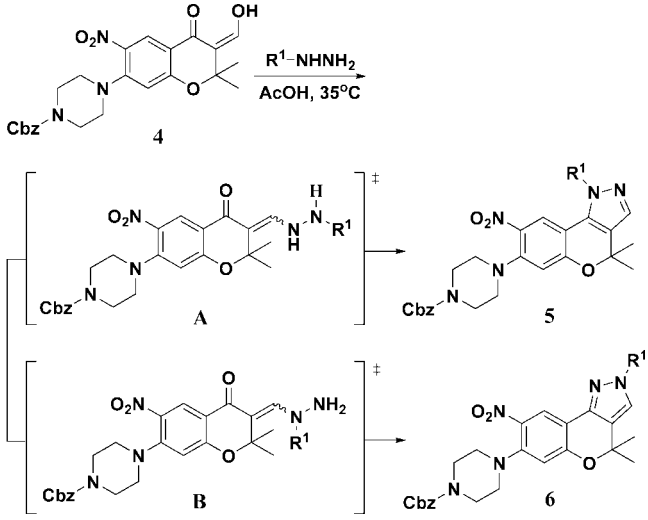
[a] Reaction Conditions: (a) KNO_3, H_2SO_4, 0°C, 2 h (59%); (b) Cbz−piperazine, acetonitrile, 40°C, overnight (99%, recovery yield); (c) $HC(OEt)_3$, $BF_3 \cdot OEt_2$, DIPEA, DCM, −78°C to r.t., 2 h (93%); (d) I_2, acetone, 35°C, overnight (84%).

s-*cis* enone as a key intermediate.[6] In this report, we focused on the construction of small-molecule library using a novel core skeleton (**VI**) in high efficiency. To maximize the structural diversity of the substituents, we introduced the three appending potentials: an R^1 diversity point at substituents on pyrazoles and R^2 and R^3 diversity points via systematic N-modifications. Molecular diversity at the R^2 and R^3 positions can be achieved by the introduction of two different amines to chromanone moiety **1**.

After considering all these facts, we initiated the synthetic route from 7-fluoro-2,2-dimethyl-2,3-dihydrochromen-4-one **1**, which undergoes nitration with potassium nitrate to introduce the aniline moiety in a masked form. In fact, the introduction of a nitro group can significantly facilitate the following nucleophilic aromatic substitution of monoprotected Cbz-piperazine at the fluoride position. We can expand the small-molecule library by the incorporation of various amines at the C-7 position, but we focused on diversification using the piperazine moiety because of its rich body of biological effects. In our previous study, electron-rich chromenones, such as methoxy-substituted 2,3-dihydrochromen-4-one, were directly transformed to hydroxy-substituted s-*cis* enone by the treatment with sodium methoxide and ethyl formate.[6] However, this wasn't applicable in the case of our electron-deficient chromenone **2**, because the acidic proton at the C-3 position was readily removed by treatment with sodium methoxide, which leads to the decomposition of benzopyran itself. Therefore, the synthetic route to hydroxy-substituted s-*cis* enone **4** included a detour via the introduction of an acetal group by treatment with triethyl orthoformate in high yield (93%).[14] The acetal deprotection of the resulting diethoxymethyl chromenone **3** was initially pursued using standard acidic hydrolysis, which can liberate the acetal moiety in the enol form, but the resulting hydroxy-substituted s-*cis* enone **4** was immediately decomposed under acidic conditions, even after screening for various acid sources. Then, we introduced an I_2-catalyzed acetal deprotection reaction,[15] which yields the desired s-*cis* enone **4** from **3** in 84% yield. On the basis of the unusual peak at 14.76 ppm of ^1H NMR spectra, the resulting hydroxy-substituted s-*cis* enone **4** exists as a Z-isomer through an internal hydrogen bonding. However, we believe that a β-keto aldehyde **4**, a tautomer of hydroxy-substituted s-*cis* enone, is the key intermediate for the condensation with hydrazines.

In our previous study, the regioselective synthesis of benzopyranylpyrazole derivatives was achieved by the condensation of a β-keto aldehyde with arylhydrazine in AcOH through the intriguing interplay of the nucleophilicity on arylhydrazines and the electrophilicity on dielectrophiles: the nucleophilicity of the terminal amine in arylhydrazine is significantly higher than that of internal amine and only allows intermediate **A** because of the conjugative participation of lone pair electrons to the aryl rings.[6] We explored the general applicability of this regioselective synthesis toward various substituents. As shown in Table 1, excellent regioselectivity was obtained in the case of 4-trifluoromethylphenyl hydrazine and phenyl hydrazine (entries 1 and 3, Table 1). However, deterioration of regioselectivity was

Table 1. Regioisomeric Ratio in the Synthesis of Benzopyranylpyrazole from the Condensation of a β-Keto Aldehyde **4** with Substituted Hydrazines

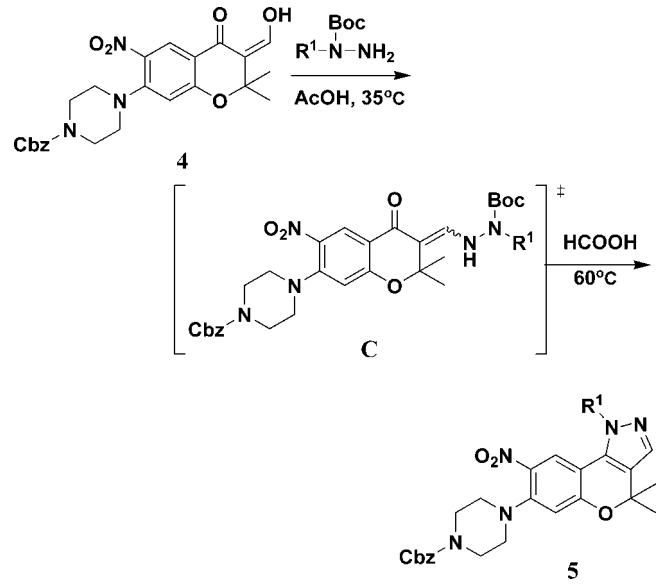


entry	R^1	product	ratio[g] (**5**/**6**)	yield
1	4-trifluoromethylphenyl	**5**{*1*}/**6**{*1*}	>99:1	86%[i]
2[a]	4-methoxyphenyl[e,f]	**5**{*2*}/**6**{*2*}	74:26[h]	74%[i]
3	phenyl	**5**{*3*}/**6**{*3*}	>99:1	93%[i]
4[a]	2,5-dimethylphenyl	**5**{*4*}/**6**{*4*}	80:20	74%[i]
5[b]	propyl[f]	**5**{*5*}/**6**{*5*}	53:47	93%[j]
6[b]	cyclopentyl[f]	**5**{*6*}/**6**{*6*}	74:26	56%[j]
7[c]	benzyl	**5**{*7*}/**6**{*7*}	93:7	91%[j]
8[b]	2-pyridylmethyl[f]	**5**{*8*}/**6**{*8*}	70:30	98%[j]
9	2-hydroxyehtyl[f]	**5**{*9*}/**6**{*9*}	55:45	93%[j]
10[d]	methyl[f]	**5**{*10*}/**6**{*10*}	56:44	97%[j]

[a] Arylhydrazine hydrochloride. [b] Alkyhydrazine trifluoroacetate. [c] Alkylhydrazine hydrochloride. [d] Alkyhydrazine sulfate. [e] EtOH, 60 °C. [f] Equal molar quantity of TEA was used to neutralize the hydrazine salt. [g] Isomeric ratio was determined by ^{1}H NMR spectroscopy or LC/MS of crude products. [h] Isomeric ratio was determined by purified yields of each regioisomer. [i] Isolated yields of major product **5**. [j] Combined yields of regioisomeric mixtures (**5** and **6**).

observed in the case of 4-methoxylphenyl hydrazine and 2,5-dimethylphenyl hydrazine (entries 2 and 4, Table 1), which indicates that the presence of electron donating groups on arylhydrazines can increase the nucleophilicity of their internal amines. Therefore, the internal amine of an arylhydrazine can actively participate in enamine formation with s-*cis* enone, which leads to the formation of the other regioisomer. We used a protic solvent, ethanol, for the condensation with 4-methoxylphenylhydrazine, because 4-methoxyphenylhydrazine itself is decomposed in AcOH. The regioisomeric ratio of the resulting pyrazoles was determined by crude ^{1}H NMR, and the structure was confirmed by nuclear Overhauser effect (NOE) experiments. In fact, the regioisomers of aryl-substituted benzopyranylpyrazoles were easily separable by silica gel flash column chromatography. However, in the case of alkylhydrazines, we obtained an inseparable regioisomeric mixture of pyrazoles (**5** and **6**) via two different mechanisms because of the similar nucleophilicity of the two nitrogen atoms in alkylhydrazine: one is the enamine formation of β-keto aldehyde **4** with the terminal amines of alkylhydrazines via intermediate **A**, and the other is that with the internal amines of alkylhydrazines via intermediate **B**. As shown in Table 1, most alkylhydrazines have no regioselectivity in the condensation with β-keto aldehyde, except the case of benzylhydrazine (entry 7, Table 1). To include alkyl-substituted benzopyranylpyrazoles in our library with secured regioselectivity, we introduced a Boc-protected alkylhydrazine group (see Supporting Information) at the internal amine position. Boc-protected alkylhydrazine can effectively block the nucleophilicity of the internal amine moiety, and then only the terminal amine of alkylhydrazine can generate the enamine intermediate **C** in acetic acid. Subsequent treatment with formic acid can successfully remove the Boc group from intermediate **C**, which converts to the desired benzopyranylpyrazole **5** with excellent regioselectivity via spontaneous intramolecular condensation in excellent yields (see Table 2). Therefore, we achieved regioselectivity in the synthesis of alkyl-substituted pyrazoles by the transient introduction of a Boc protecting group at the internal amine of alkylhydrazines, instead of modulating the reactivity of the 1,3-dicarbonyl moiety. This was suitable for general application to robust library construction.

Table 2. Regioisomeric Ratio in the Synthesis of Benzopyranylalkylpyrazole from a β-Keto Aldehyde **4** with Boc-Protected Alkylhydrazines



entry	R^1	product	ratio(**5**/**6**)[a]	yield[b]
1	propyl	**5**{*5*}/**6**{*5*}	>99:1	93%
2	cyclopentyl	**5**{*6*}/**6**{*6*}	>99:1	95%
3	benzyl	**5**{*7*}/**6**{*7*}	>99:1	97%
4	2-pyridiylmethyl	**5**{*8*}/**6**{*8*}	>99:1	94%

[a] Regioisomeric ratio was determined by LC/MS of crude product. [b] Isolated yields of major product **5**.

After the establishment of regioselective synthetic protocols for alkyl- and aryl-substituted benzopyranylpyrazoles, we then focused on maximizing the molecular diversity of the small-molecule library. We already introduced diversity at the R^1 position from substituted hydrazines, and we can further modify this molecular frame by amine modification at the R^2 and R^3 positions.

Selection of Building Blocks Using Chemoinformatics. To establish diversity in our core skeletons, various types of diversification on piperazinyl secondary amine or aniline can be applied with a vast number of building blocks, and combinatorial modification at the R^2 and R^3 positions can produce an unlimited number of compounds. However, we

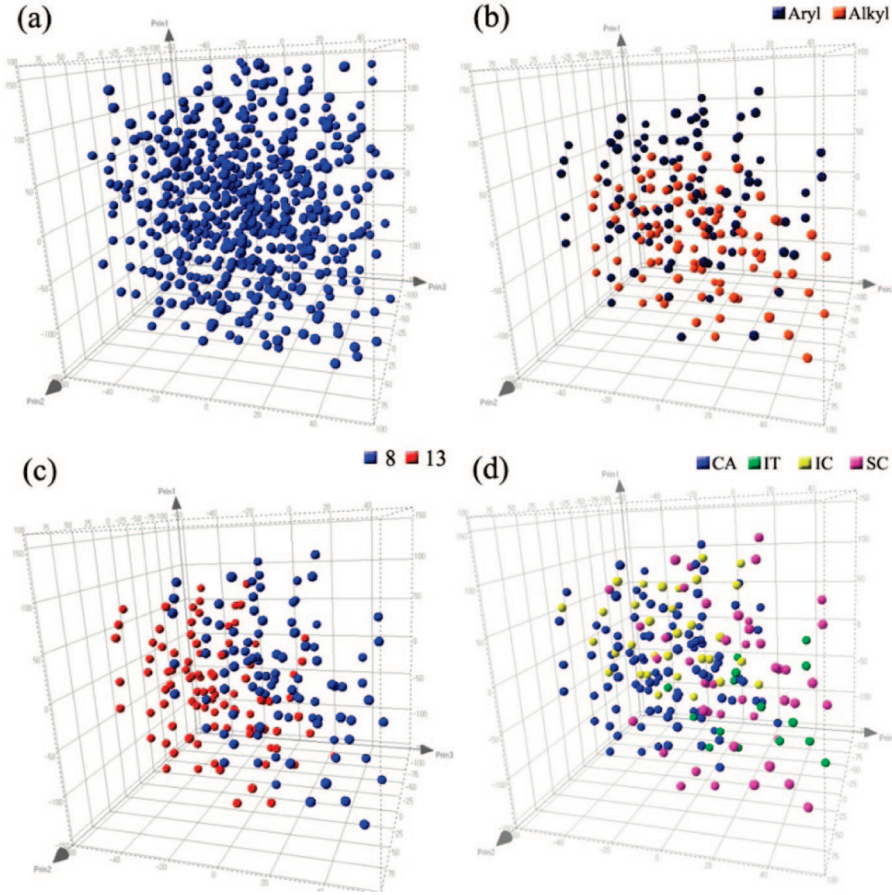
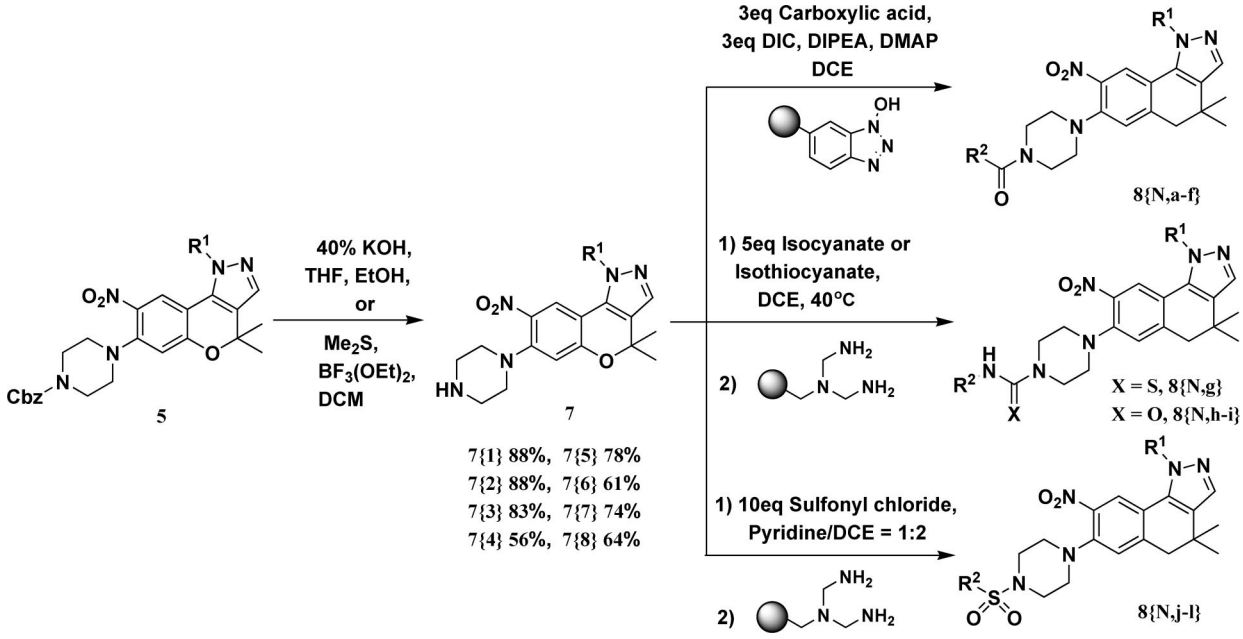


Figure 2. Chemoinformatic analysis of molecular diversity toward the rational selection of building blocks for the construction of a benzopyranylpyrazole library. (a) 3-D visualization of chemical space of 696-member virtual library. (b) Selected collection of small molecules color-coded by two different substituents on the R^2 position. (c) Selected collection of small molecules color-coded by two different core skeletons (**8** and **13**). (d) Selected collection of small molecules color-coded by different N-modifications at R^2 and R^3 positions [CA, carboxylic acids; IT, isothiocyanates; IC, isocyanates; SC, sulfonyl chlorides].

decided to pursue the rational construction of a pilot library of benzopyranylpyrazoles through orthogonal single modification either at the R^2 or R^3 position, without pursuing full library construction through the matrix approach. Under these circumstances in the construction of a pilot library with appending potentials, we would like to maximize molecular diversity; therefore, we exercised the chemoinformatic protocols for the rational selection of building blocks at the R^1, R^2, and R^3 positions. First, we constructed a 696-member virtual library of benzopyranylpyrazoles using 41 available building blocks, including 12 hydrazines, 12 carboxylic acids, 4 isothiocyanates, 6 isocyanates, and 7 sulfonyl chlorides. Then, we prioritized the building blocks to maximize the molecular diversity of the benzopyranylpyrazole library in the chemical space through the development of a diversity matrix with 15 major molecular descriptors using PreADMET 2.0 [BMDRC, Seoul, Korea] and visualized with three principal components (Prin) calculated using SAS 9.1 [SAS Institute Inc., Cary, NC]. The three principal components (Prin1, Prin2, and Prin3) represent together 93.7% of the total variance in molecular descriptors. The Prin1 factor, which explains 64.0% of the total variance, is mainly constituted by molecular weight (MW), van der Waals (VDW) surface, and hydrophobic VDW surface area. The Prin2 factor, which explains 22.2% of the total variance, is influenced by molecular weight (MW), polar VDW surface area, topological polar surface area, and H-bond acceptor surface area. The Prin3 factor, accounting for 7.5% of the total variance, includes H-bond acceptor surface area, polar VDW surface area, and topological polar surface area. Prin1 represents the diversity within the same class of core skeletons in terms of molecular size and lipophilic descriptors, and Prin2 and Prin3 differentiate molecular diversity by the polar surface area and hydrogen acceptor. From the primary chemical space in 3-D (Figure 2a), we eliminated redundant data points and prioritized the building blocks that contribute to the conservation of molecular diversity with a reduced number of molecules in the 3-D chemical space (Figure 2b−d; also see Supporting Information). In our computational exercise, it was observed that the two different skeletons, alkyl- and aryl-substituted benzopyranylpyrazoles, can efficiently distribute library members in the different regions of the 3-D chemical space as well as the different modification strategy on secondary amines (**8**) and anilines (**13**) with various substitutents (carboxylic acids, isothiocyanates, isocyanates, and sulfonyl chlorides) on the R^2 and R^3 positions (Figure 2b−d). Among these building blocks, four arylhydrazines and four alkylhydrazines were selected to introduce diversity at the R^1 position of the benzopyranylpyrazole core skeletons. We introduced diversity at the R^2 and R^3 positions with the same set of substitutents [six carboxylic acids, one isothiocyanate, two isocyanates, and

Scheme 2. Synthetic Strategy for the Diversification at R^2 through Solution-Phase Parallel Synthesis Using Solid-Phase Reagents



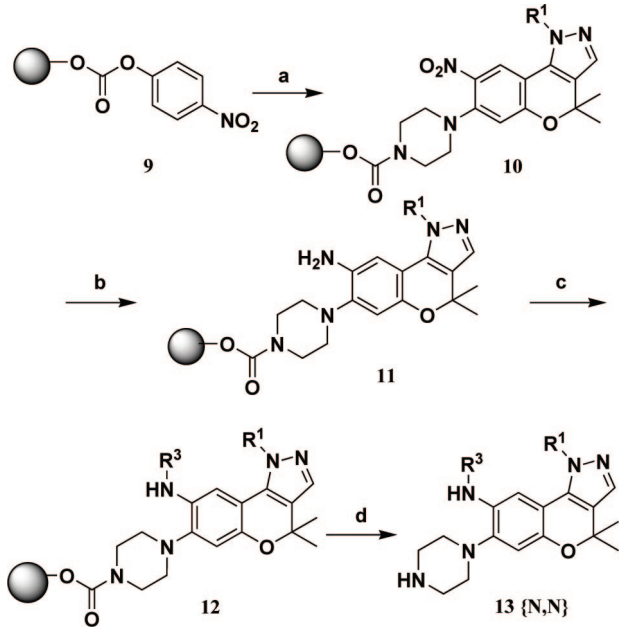
three sulfonyl chlorides] to allow systematic comparison of the two different skeletons (**8** and **13**). This would maximize chemical diversity with the relatively small members of the benzopyranylpyrazole library.

Efficient Construction of 192-Member Benzopyranylpyrazole Library via Solution-Phase and Solid-Phase Parallel Synthesis. After the establishment of a regioselective synthetic procedure for benzopyranylpyrazoles and the rational selection of building blocks to maximize the chemical diversity with the smallest collection of substituents, we pursued efficient library realization using parallel synthesis. The alkyl- and aryl-substituents were introduced at the R^1 position by regioselective synthesis of pyrazole intermediates **5**{*1*}−**5**{*8*} in high-to-excellent yields. The pyrazole intermediates were then subjected to extensive diversification in a parallel fashion: the R^2 position was efficiently modified with various substituents in solution phase using solid-phase reagents, and the R^3 position was practically diversified through the immobilization of the piperazinyl secondary amine on a solid support. To orthogonally modify aniline and piperazine, we pursued the mild deprotection of the Cbz group on the piperazine moiety, not by catalytic hydrogenolysis. Therefore, the Cbz group was removed from pyrazole intermediate **5** by 40% KOH[16] [for **5**{*1*}−**5**{*4*}] or dimethyl sulfate and $BF_3 \cdot OEt_2$[17] [for **5**{*5*}−**5**{*8*}] to yield the deprotected pyrazoles **7**{*1*}−**7**{*8*}, which were subjected to the further diversification in efficient parallel synthesis.

First, we modified the piperazine moiety of benzopyranylpyrazoles **7** using solid-phase reagents: (1) direct modification with an activated ester on a solid support, which was generated by the treatment of HOBt-6-carboxamidomethyl polystyrene with carboxylic acids, *N*,*N*′-diisopropylcarbodiimide (DIC), diisopropylethylamine (DIPEA), and 4-dimethylaminopyridyl (DMAP) for 15 h at room temperature;[18] (2) solution-phase modification with either sulfonyl chloride, isocyanate, or isothiocyanate on a secondary amine, followed by removal of excess reagents with PS-trisamine as a scavenger resin.[19] As shown in Scheme 2, the piperazine moiety of the benzopyranylpyrazoles was transformed into amide, sulfonamide, urea, and thiourea with six carboxylic acids, three sulfonyl chlorides, two isocyanates, and one isothiocyanate to maximize the chemical diversity of the small molecules. The diversification at the R^2 position using solution-phase parallel synthesis yielded about 10 mg of final product as a library member without further purification. After the library construction, an aliquot of each library member was injected onto a LC/MS with a PDA detector to determine the identity and purity of the final compounds. The presence of all desired compounds was unambiguously confirmed by their molecular mass and the average purity of the final 96 compounds with R^2 diversification was 91%.

To modify the aniline group at the R^3 position, we utilized solid-phase parallel protocols to maximize the efficiency of diversification without the requirement for further purification. As shown in Scheme 3, Wang resin was activated with *p*-nitrophenylchloroformate in the presence of DIPEA, followed by the loading of Cbz-deprotected benzopyranylpyrazole intermediates **7**{*1*}−**7**{*8*} on the solid support. The nitro group on resin-bound intermediates **10** was reduced with 2 M tin (II) chloride dihydrate in DMF.[20] The resulting resin-bound aniline moiety **11** was subsequently diversified with an identical set of 12 building blocks as that used for the modification at the R^2 position. The synthetic procedures were modified to accommodate the different strategies in solution-phase parallel synthesis using solid-phase reagents as against those in solid-phase parallel synthesis. For instance, the aniline moiety was coupled with various carboxylic acids activated by the coupling reagent PyBOP for amide formation.[21] The aniline group was also modified by the treatment of isocyanates or isothiocyanates with anhydrous triethylamine (TEA) in dichloroethane (DCE) and sulfonyl chlorides with anhydrous pyridine for 24 h for the formation of urea, thiourea, and sulfonamide moieties.[22] The final cleavage step was performed under 50% trifluoroacetic acid (TFA) in

Scheme 3. Synthetic Strategy for the Diversification on Aniline Moiety at R^3 Position through Solid-Phase Parallel Synthesis[a]



[a] (a) Benzopyranylpyrazoles **7**{*1*}−7{*8*}, DMF, 24 h; (b) 2 M $SnCl_2 \cdot (H_2O)_2$ in DMF; (c) (i) carboxylic acids, PyBOP, DMAP, 3% NMM in DMF, 24 h; (ii) isocyanates, TEA, DCE, 24 h; (iii) sulfonyl chloride (Pyr/DCE=1:2), 24 h; (d) 50% TFA in DCM, 1 h.

dichloromethane to liberate various benzopyranylpyrazoles **13** substituted at the R^3 position. The diversification at the R^3 position using solid-phase parallel synthesis yielded about 10 mg of final product as a library member without further purification. An identical characterization procedure was applied to this set of 96 compounds, and the presence of all desired compounds was unambiguously confirmed by their molecular mass. The purities of the final 96 compounds with R^3 diversification are listed in Table 4 in different colors. Overall, the average purity of the final 96 compounds with R^3 diversification was 84%. The biggest difference we noticed during the diversification at the R^3 position was that the purities of compounds modified with methyl isothiocyanate (**13**{*1*,*g*}−**13**{*8*,*g*}) were much lower than the average purities, and even lower than the purities of the compounds modified with same methyl isothiocyanate at the R^2 position (**8**{*1*,*g*}−**8**{*8*,*g*}). This might be caused by the instability of the thiourea moiety in 50% TFA during the final cleavage step. As shown in Table 5, the representative compounds of the benzopyranylpyrazole library were characterized in the crude products by ^1H and gradient-correlated spectroscopy (gCOSY) NMR spectroscopy (see Supporting Information).

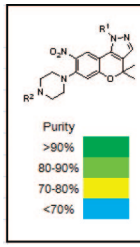
Conclusion

In our study, the practical construction of a pilot library with benzopyranylpyrazole, a novel core skeleton synthesized through the recombination of privileged structures, benzopyran and pyrazole, was successfully conducted through the efficient utilization of solution-phase parallel synthesis using solid-phase reagents and solid-phase parallel synthesis. The diversity of this core skeleton was expanded by the introduction of alkyl- and aryl-substituent at the R^1 position, which was possible through the development of novel procedures for the regioselective synthesis of aryl- and alkyl-substituted pyrazoles: (1) the regioselective condensation of a β-keto aldehydes by the intriguing nucleophilicity difference under acetic acid in the case of arylhydrazines and (2) the efficient blocking of nucleophilicity on the internal amine with the Boc group, followed by spontaneous deprotection and condensation under formic acid in the case of alkylhydrazines. With regioselective synthetic methods for benzopyranylpyrazoles in hand, we further diversified our core skeleton by the introduction of a piperazine moiety, which provided the R^2 diversity point. The introduction of a nitro group on the benzopyran moiety can accelerate the nucleophilic aromatic substitution of secondary amines and provide the R^3 diversity point at the aniline moiety through the reduction of the nitro group. For this pilot library, we only focused diversification at the R^1 position with either the R^2 or R^3 position and thus maximized its diversity through the rational selection of building blocks using chemoinformatics. The simplified and highly efficient synthetic protocols were tolerant to various building blocks. This eliminated tedious building block rehearsals and a 192-member benzopyranylpyrazole pilot library was constructed. Overall, the average purity of the library is 87%. We are currently pursuing biological evaluations of the benzopyranylpyrazole library, which will guide us toward untouched amine diversification, especially through the matrix approach at both the R^2 and R^3 positions for focused library construction or full library realization.

Experimental Section

General Information. All commercially available reagents and solvents were used without further purification unless noted otherwise. Pyridine (pyr) was dried by distillation from potassium hydroxide immediately prior to use. Dichloromethane (DCM) was dried by distillation from CaH_2, and dichloroethane (DCE) was dried by activated molecular sieve (MS; 4Å). Other solvents and organic reagents were purchased from commercial venders and used without further purification unless otherwise mentioned. Wang resins, polystyrene-trisamine (PS-Trisamine), and HOBt-6-carboxamidomethyl polystyrene (PS-HOBt) were obtained from Novabiochem. ^1H and ^{13}C NMR spectra were obtained on 500 MHz FT-NMR spectrophotometer. Chemical shifts are reported in parts per million relative to the residual solvent peak for $CDCl_3$ (^1H, 7.27; ^{13}C, 77.23) and CD_3OD (^1H, 3.31; ^{13}C, 49.15). Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), br s (broad singlet), etc. Coupling constants are reported in hertz. The reaction steps for library construction were performed in parallel using the FlexChem Synthesis System from SciGene [Sunnyvale, CA] in a 96-deep-well filtration block. The reaction volume per well in the 96-well reaction block was set to 1.2 mL unless noted otherwise. The purity of all the library members was observed by a LC/MS system equipped with a reverse-phase column (C-18, 50 × 2.1 mm, 5 μm) and photodiode array (PDA) detector using electron spray ionization (ESI). The regioisomeric ratio of benzopy-

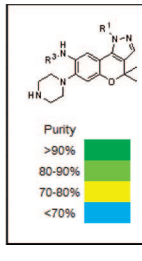
Table 3. Sets of Building Blocks and Purities of Benzopyranylpyrazoles **8**



		R²	a	b	c	d	e	f	g	h	i	j	k	l
R¹	4-Trifluoromethylphenyl	1	8{1,a}	8{1,b}	8{1,c}	8{1,d}	8{1,e}	8{1,f}	8{1,g}	8{1,h}	8{1,i}	8{1,j}	8{1,k}	8{1,l}
	4-Methoxyphenyl	2	8{2,a}	8{2,b}	8{2,c}	8{2,d}	8{2,e}	8{2,f}	8{2,g}	8{2,h}	8{2,i}	8{2,j}	8{2,k}	8{2,l}
	Phenyl	3	8{3,a}	8{3,b}	8{3,c}	8{3,d}	8{3,e}	8{3,f}	8{3,g}	8{3,h}	8{3,i}	8{3,j}	8{3,k}	8{3,l}
	2,5-Dimethylphenyl	4	8{4,a}	8{4,b}	8{4,c}	8{4,d}	8{4,e}	8{4,f}	8{4,g}	8{4,h}	8{4,i}	8{4,j}	8{4,k}	8{4,l}
	Propyl	5	8{5,a}	8{5,b}	8{5,c}	8{5,d}	8{5,e}	8{5,f}	8{5,g}	8{5,h}	8{5,i}	8{5,j}	8{5,k}	8{5,l}
	Cyclopentyl	6	8{6,a}	8{6,b}	8{6,c}	8{6,d}	8{6,e}	8{6,f}	8{6,g}	8{6,h}	8{6,i}	8{6,j}	8{6,k}	8{6,l}
	Benzyl	7	8{7,a}	8{7,b}	8{7,c}	8{7,d}	8{7,e}	8{7,f}	8{7,g}	8{7,h}	8{7,i}	8{7,j}	8{7,k}	8{7,l}
	2-Pyridylmethyl	8	8{8,a}	8{8,b}	8{8,c}	8{8,d}	8{8,e}	8{8,f}	8{8,g}	8{8,h}	8{8,i}	8{8,j}	8{8,k}	8{8,l}

[a] Purities were obtained by LC/MS analysis of final products without further purification.

Table 4. Sets of Building Blocks and Purities of Benzopyranylpyrazoles **13**



		R³	a	b	c	d	e	f	g	h	i	j	k	l
R¹	4-Trifluoromethylphenyl	1	13{1,a}	13{1,b}	13{1,c}	13{1,d}	13{1,e}	13{1,f}	13{1,g}	13{1,h}	13{1,i}	13{1,j}	13{1,k}	13{1,l}
	4-Methoxyphenyl	2	13{2,a}	13{2,b}	13{2,c}	13{2,d}	13{2,e}	13{2,f}	13{2,g}	13{2,h}	13{2,i}	13{2,j}	13{2,k}	13{2,l}
	Phenyl	3	13{3,a}	13{3,b}	13{3,c}	13{3,d}	13{3,e}	13{3,f}	13{3,g}	13{3,h}	13{3,i}	13{3,j}	13{3,k}	13{3,l}
	2,5-Dimethylphenyl	4	13{4,a}	13{4,b}	13{4,c}	13{4,d}	13{4,e}	13{4,f}	13{4,g}	13{4,h}	13{4,i}	13{4,j}	13{4,k}	13{4,l}
	Propyl	5	13{5,a}	13{5,b}	13{5,c}	13{5,d}	13{5,e}	13{5,f}	13{5,g}	13{5,h}	13{5,i}	13{5,j}	13{5,k}	13{5,l}
	Cyclopentyl	6	13{6,a}	13{6,b}	13{6,c}	13{6,d}	13{6,e}	13{6,f}	13{6,g}	13{6,h}	13{6,i}	13{6,j}	13{6,k}	13{6,l}
	Benzyl	7	13{7,a}	13{7,b}	13{7,c}	13{7,d}	13{7,e}	13{7,f}	13{7,g}	13{7,h}	13{7,i}	13{7,j}	13{7,k}	13{7,l}
	2-Pyridylmethyl	8	13{8,a}	13{8,b}	13{8,c}	13{8,d}	13{8,e}	13{8,f}	13{8,g}	13{8,h}	13{8,i}	13{8,j}	13{8,k}	13{8,l}

[a] Purities were obtained by LC/MS analysis of final products without further purification.

Table 5. Purity and Mass of Representative Members of Benzopyranylpyrazole Library

	R¹	R²	R³	purity (%)	MS (calcd)	MS (found)
8{*1*,*a*}	4-trifluoromethylphenyl	benzoyl		95.4	578.19	578.16
8{*2*,*j*}	4-methoxyphenyl	dimethylsulfamoyl		96.2	543.19	543.14
8{*3*,*a*}	phenyl	benzoyl		94.6	510.21	510.14
8{*4*,*a*}	2,5-dimethylphenyl	benzoyl		96.6	538.24	538.15
8{*5*,*b*}	propyl	3-phenylpropanoyl		96.8	476.22	476.16
8{*5*,*c*}	propyl	3-(thiophen-2-yl)acryloyl		95.4	508.19	508.16
8{*6*,*j*}	cyclopentyl	dimethylsulfamoyl		95.9	505.22	505.14
8{7,a}	benzyl	benzoyl		93.2	524.22	524.17
8{8,h}	2-pyridylmethyl	cyclohexylcarbamoyl		97.7	546.28	546.22
13{*3*,*a*}	phenyl		benzoyl	94.4	480.23	480.15
13{*5*,*e*}	propyl		3-methylbut-2-enoyl	91.7	424.26	424.18
13{*6*,*c*}	cyclopentyl		3-(thiophen-2-yl)acryloyl	91.4	504.24	504.21
13{*8*,*b*}	2-pyridylmethyl		3-phenylpropanoyl	97.0	523.32	523.32

ranylpyrazoles was observed on HPLC/MS spectra recorded using a Hewlett-Packard HP-1100 HPLC system, which comprised a Quadrupole-TOF mass spectrometer, PDA detector with a Shiseido capcell pak column (C-18, 250 × 4.6 mm, 5 μm). The products were purified by flash column chromatography on silica gel (230−400 mesh). The eluent used for purification is reported in parentheses. Thin-layer chromatography (TLC) was performed on precoated glass-backed plates (silica gel 60 F254 0.25 mm), and components were visualized by observation under UV light (254 and 365 nm) or by treating the plates with anisaldehyde, ninhydrine, and vaniline, followed by thermal visualization. Double-deionized water (ddH_2O) was prepared by ion exchange and filtration.

Benzyl 4-(2,2-Dimethyl-6-nitro-4-oxo-3,4-dihydro-2*H*-chromen-7-yl)piperazine-1-carboxylate (2). To a solution of 7-fluoro-2,2-dimethyl-2,3-dihydrochromen-4-one **1** (4.0 g, 20.6 mmol) in c-H_2SO_4 (50 mL) at 0 °C, KNO_3 (2.52 g, 22.6 mmol) was added slowly. After it was stirred at 0 °C for 2 h, the reaction mixture was poured into ice water. The yellowish solid was filtered and washed with several portions of cold water. The resulting solid was purified by recrystallization in DCM to obtain 7-fluoro-2,2-dimetyl-6-nitrochroman-4-one in 59% yield as a yellow solid. To a solution of 7-fluoro-2,2-dimetyl-6-nitrochroman-4-one (1.8 g, 7.86 mmol) in 40 mL of acetonitrile, mono-Cbz-protected piperazine (2 g, 9.43 mmol) was added and stirred at 40 °C for 13 h. After the completion of reaction, as monitored by TLC, the reaction mixture was condensed under reduced pressure, and the condensed reaction mixture was redissolved in DCM. The organic layer was washed with 1 N HCl (aq) and brine and dried over anhydrous $MgSO_4$. The filtrate was condensed under reduced pressure, and the resulting mixture was purified by silica gel flash column chromatography to provide the desired product **2** as a yellow solid (99%, recovery yield, 1.86 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.39−7.33 (m, 5H), 6.43 (s, 1H), 5.17 (s, 2H), 3.72−3.67 (m, 4H), 3.12 (br s, 4H), 2.72 (s, 2H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.6, 163.5, 155.4, 152.0, 136.6, 135.9, 128.8, 128.4, 128.2, 127.7, 113.2, 107.3, 81.2, 67.7, 48.6, 27.0; MS (ESI+) *m*/*z* calcd for $C_{23}H_{25}N_3O_6$ $[M + H]^+$ 440.17, found *m*/*z* 440.14.

Benzyl 4-(3-(Diethoxymethyl)-2,2-dimethyl-6-nitro-4-oxo-3,4-dihydro-2*H*-chromen-7-yl)piperazine-1-carboxylate (3). To a solution of triethyl orthoformate (3.65 mL, 21.9 mmol) in DCM (20 mL), $BF_3 \cdot OEt_2$ (2.75 mL, 21.9 mmol) was slowly added over a period of 10 min at −10 °C under an argon atmosphere. The reaction mixture was

then gradually warmed up to 0 °C. After 15 min of stirring at 0 °C, the reaction mixture was cooled back to −78 °C. To this reaction mixture, **2** (3.2 g, 7.3 mmol) in 5 mL of DCM was added, and DIPEA (4.5 mL, 25.5 mmol) was then added slowly over 30 min. The resulting mixture was stirred at −78 °C for 10 min, and then warmed up to room temperature for an additional 2 h of stirring. The resultant mixture was diluted with DCM and washed with sat. $NaHCO_3$(aq) solution. The combined organic layer was dried over anhydrous $MgSO_4$ and condensed under reduced pressure. The resulting mixture was purified by silica gel flash column chromatography to provide the desired product **3** as a yellow solid (3.46 g, 87%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.39−7.31 (m, 5H), 6.41 (s, 1H), 5.17 (s, 2H), 4.90 (d, J = 5.4 Hz, 1H), 3.76−3.61 (m, 6H), 3.55−3.40 (m, 2H), 3.11 (br s, 4H), 2.82 (d, J = 5.5 Hz, 1H), 1.56 (s, 3H), 1.43 (s, 3H), 1.18 (t, J = 7.0 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3, 162.8, 155.4, 151.8, 136.6, 135.9, 128.8, 128.4, 128.2, 127.7, 113.8, 107.0, 99.8, 82.8, 67.6, 63.3, 62.1, 58.6, 50.9, 43.6, 26.8, 25.8, 15.3, 15.2; MS (ESI+) *m*/*z* calcd for $C_{28}H_{35}N_3O_8$ $[M + H]^+$ 542.24, found *m*/*z* 542.24.

Benzyl 4-(3-(Hydroxymethylene)-2,2-dimethyl-6-nitro-4-oxo-3,4-dihydro-2*H*-chromen-7-yl)piperazine-1-carboxylate (4). To a solution of diethoxymethyl chromenone **3** (3.45 g, 6.38 mmol) in acetone (100 mL), iodine (324 mg, 0.2 mmol) was added in one portion and the reaction mixture was stirred at 35 °C for 14 h. After reaction completion, as monitored by TLC, the solvent was removed under reduced pressure. The resultant was diluted with DCM and washed sequentially with 5% aqueous $Na_2S_2O_3$, ddH_2O, and brine. The organic layer was dried over anhydrous $MgSO_4$ and filtered. Then, the filtrate was condensed under reduced pressure, and the resulting mixture was purified by silica gel flash column chromatography to provide the desired product **4** as a yellow solid (2.5 g, 84%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.76 (d, J = 7.5 Hz, 1H), 8.48 (s, 1H), 7.89 (d, J = 7.0 Hz, 1H), 7.41−7.30 (m, 5H), 6.40 (s, 1H), 5.17 (s, 2H), 3.73−3.67 (m, 4H), 3.14 (br s, 4H), 1.62 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.9, 169.8, 162.4, 155.4, 151.8, 136.6, 135.9, 128.8, 128.4, 128.2, 127.4, 113.6, 112.2, 107.1, 80.5, 67.7, 50.9, 43.6, 28.8; MS (ESI+) *m*/*z* calcd for $C_{24}H_{25}N_3O_7$ $[M + H]^+$ 468.17, found *m*/*z* 468.14.

General Procedure for the Synthesis of Aryl-Substituted Benzopyranylpyrazoles 5{*1*}−5{*4*}. To a solution of arylhydrazine (1.2 equiv) in AcOH (0.1 M), hydroxy-substituted s-*cis* enone **4** was added carefully and was stirred for 2 h at 35 °C. The reaction mixture was diluted with DCM, followed by aqueous workup with sat. Na_2CO_3(aq) and brine. The aqueous layer was extracted with DCM three times. The combined organic layer was dried over anhydrous $MgSO_4$ and condensed under reduced pressure. The resulting mixture was purified by silica gel flash column chromatography. In the case of 4-methoxyphenyl hydrazine hydrochloride for the condensation with hydroxy-substituted s-*cis* enone **4**, the reaction was performed in EtOH at 70 °C after the neutralization of the hydrochloride salt with TEA (1.2 equiv) because of the instability of 4-methoxyphenyl hydrazine in acetic acid.

Characterization of Compound 5{*1*}: 86% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1H 7.83 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.63 (s, 1H), 7.55 (s, 1H), 7.40−7.33 (m, 5H), 6.65 (s, 1H), 5.17 (s, 2H), 3.71−3.66 (m, 4H), 3.06 (br s, 4H), 1.70 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 155.4, 148.7, 142.7, 136.7, 135.4, 135.3, 130.6, 128.7, 128.3, 128.1, 127.0, 126.1, 123.5, 121.6, 109.4, 108.5, 79.6, 67.5, 51.6, 43.8, 29.2; MS (ESI+) *m*/*z* calcd for $C_{31}H_{28}F_3N_5O_5$ $[M + H]^+$ 608.58, found *m*/*z* 608.31.

Characterization of Compound 5{*2*}: 79% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52(s, 1H), 7.47 (s, 1H), 7.42−7.31 (m, 7H), 7.05 (dd, J = 6.8, 2.3 Hz), 6.61 (s, 1H), 5.17 (s, 2H), 3.91 (s, 3H), 3.70−3.65 (m, 4H), 3.03 (br s, 4H), 1.70 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 157.9, 155.4, 148.4, 136.7, 135.5, 134.1, 132.7, 130.5, 128.7, 128.3, 128.1, 127.6, 121.9, 121.5, 115.0, 109.19, 109.17, 79.8, 67.5, 55.9, 51.7, 43.8, 29.5; MS (ESI+) *m*/*z* calcd for $C_{31}H_{31}N_5O_6$ $[M + H]^+$ 570.23, found *m*/*z* 570.22.

Characterization of Compound 5{*3*}. 93% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58−7.54 (m, 3H), 7.53 (s, 1H), 7.51−7.47 (m, 3H), 7.39−7.33 (m, 5H), 6.62 (s, 1H), 5.17 (s, 2H), 3.70−3.66 (m, 4H), 3.04 (br s, 4H), 1.70 (s, 6H);^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 155.4, 148.5, 139.8, 136.7, 135.5, 134.5, 130.5, 129.9, 129.7, 128.7, 128.3, 128.1, 126.2, 122.4, 121.7, 109.2, 109.0, 79.8, 67.5, 51.6, 43.9, 29.5; MS (ESI+) *m*/*z* calcd for $C_{30}H_{29}N_5O_5$ $[M + H]^+$ 540.22, found *m*/*z* 540.22.

Characterization of Compound 5{*4*}: 74% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.40−7.28 (m, 7H), 7.21−7.16 (m, 2H), 6.59 (s, 1H), 5.16 (s, 2H), 3.68−3.64 (m, 4H), 3.01 (br s, 4H), 2.39 (s, 3H), 1.98 (s, 3H), 1.73 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 155.4, 148.5, 138.6, 137.5, 136.7, 135.7, 134.0, 132.7, 131.4, 131.3, 130.8, 128.7, 128.3, 128.2, 128.1, 120.9, 120.8, 109.0, 108.9, 80.0, 67.5, 51.6, 44.0, 29.8, 20.9, 16.9; MS (ESI+) *m*/*z* calcd for $C_{32}H_{33}N_5O_5$ $[M + H]^+$ 568.25, found *m*/*z* 568.70.

General Procedure for the Synthesis of Alkyl-Substituted Benzopyranylpyrazoles 5{*5*}−5{*8*}. To a solution of Boc-protected alkylhydrazine (1.2 equiv) in AcOH (10 mL), hydroxy-substituted s-*cis* enone **4** (500 mg, 1.07 mmol) was added, and the mixture was stir-heated at 35 °C for 1.5 h. After the completion of enamine formation, as monitored by TLC, formic acid (10 mL) was added and stirred at 60 °C for 1.5 h, which lead to Boc deprotection, followed by condensation. The resulting yellow solution was diluted with DCM and H_2O. The reaction mixture was neutralized with Na_2CO_3 until the solution became slightly basic. The aqueous layer was extracted with DCM three times. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated to afford a crude mixture, which was purified by silica gel flash column chromatography.

Characterization of Compound 5{*5*}: 93% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.40−7.31 (m, 5H), 7.29 (s, 1H), 6.65 (s, 1H), 5.18 (s, 2H), 4.36 (t, J = 7.5 Hz, 2H), 3.76−3.69 (m, 4H), 3.09 (br s, 4H), 1.95 (sextet, J = 7.5 Hz, 2H), 1.64 (s, 6H), 1.03 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 155.4, 148.7, 136.7, 135.3, 132.3, 129.4, 128.7, 128.3, 128.2, 121.8, 121.4, 109.6, 109.4,

79.8, 67.6, 53.4, 51.7, 43.9, 29.5, 23.6, 11.3; MS (ESI+) *m/z* calcd for $C_{27}H_{31}N_5O_5$ $[M + H]^+$ 506.23, found *m/z* 506.10.

Characterization of Compound 5{*6*}: 95% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.39−7.31 (m, 5H), 7.29 (s, 1H), 6.66 (s, 1H), 5.18 (s, 2H), 5.02−4.95 (m, 1H), 3.74−3.70 (m, 4H), 3.09 (br s, 4H), 2.30−2.15 (m, 4H), 1.99−1.92 (m, 2H), 1.80−1.74 (m, 2H), 1.63 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 155.4, 148.5, 136.7, 135.3, 131.9, 129.5, 128.7, 128.3,128.1, 121.9, 121.6, 110.1, 109.5, 79.6, 67.5, 61.9, 51.7, 44.0, 33.0, 29.3, 24.8; MS (ESI+) *m/z* calcd for $C_{29}H_{33}N_5O_5$ $[M + H]^+$ 532.25, found *m/z* 532.90.

Characterization of Compound 5{*7*}: 97% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.39 (s, 1H), 7.37−7.32 (m, 6H), 7.28−7.26 (m, 2H), 7.21 (d, J = 7.5 Hz, 2H), 6.58 (s, 1H), 5.61 (s, 2H), 5.15 (s, 2H), 3.68−3.66 (m, 4H), 3.02 (br s, 4H), 1.65 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 155.4, 148.7, 136.7, 136.1, 135.1, 132.9, 130.1, 129.2, 128.7, 128.3, 128.2, 128.1, 126.8, 122.2, 122.0, 109.1, 109.0, 79.7, 67.5, 55.4, 51.6, 43.9, 29.5; MS (ESI+) *m/z* calcd for $C_{31}H_{31}N_5O_5$ $[M + H]^+$ 554.23, found *m/z* 554.00.

Characterization of Compound 5{*8*}: 94% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (ddd, J = 4.9, 1.7, 1.0 Hz, 1H), 8.33 (s, 1H), 7.65 (dt, J = 7.7, 2.0 Hz, 1H), 7.40 (s, 1H), 7.38−7.31 (m, 5H), 7.23 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 6.60 (s, 1H), 5.71 (s, 2H), 5.16 (s, 2H), 3.70−3.66 (m, 4H), 3.03 (br s, 4H), 1.65 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 156.0, 155.4, 150.0, 148.5, 137.4, 136.7, 135.7, 133.3, 130.7, 128.7, 128.3, 128.1, 123.2, 122.2, 122.1, 121.8, 109.1, 79.6, 67.5, 57.2, 51.6, 43.9, 29.4; MS (ESI+) *m/z* calcd for $C_{30}H_{30}N_6O_5$ $[M + H]^+$ 555.23, found *m/z* 555.20.

General Procedure for Cbz-Deprotection of Aryl-Substituted Benzopyranylpyrazole 7{*1*}−7{*4*}. As a slight modification to the previously reported method,[16] 40% aqueous KOH (10 equiv) was added to a solution of Cbz-protected benzopyranylpyrazoles [**5**{*1*}−**5**{*4*}] in THF (0.5 mL) and EtOH (0.1 M), and the reaction mixture was stir-heated at 100 °C for 7 h. The resultant was diluted with DCM and washed with ddH_2O and brine. The aqueous layer was extracted with DCM three times. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated to afford a crude mixture which was purified by silica gel flash column chromatography.

Characterization of Compound 7{*1*}: 88% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.59 (s, 1H), 7.53 (s, 1H), 6.66 (s, 1H), 3.09−3.01 (m, 8H), 1.69 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 149.2, 142.8, 135.4, 135.1, 130.9, 127.0, 126.1, 123.4, 122.7, 121.8, 109.0, 107.8, 79.5, 52.7, 46.0, 29.3; MS (ESI+) *m/z* calcd for $C_{23}H_{22}F_3N_5O_3$ $[M + H]^+$ 474.17, found *m/z* 474.10.

Characterization of Compound 7{*2*}: 88% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.46 (s, 1H), 7.03 (dd, J = 6.8, 2.3 Hz, 2H), 7.38 (dd, J = 6.8, 2.3 Hz, 2H), 6.62 (s, 1H), 3.90 (s, 3H), 3.03 (s, 8H), 1.69 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 157.8, 148.7, 135.2, 134.1, 132.8, 130.7, 127.6, 121.8, 121.5, 115.0, 108.8, 108.6, 79.6, 55.8, 52.5, 45.8, 29.5; MS (ESI+) *m/z* calcd for $C_{23}H_{25}N_5O_4$ $[M + H]^+$ 436.19, found *m/z* 436.15.

Characterization of Compound 7{*3*}: 83% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59−7.45 (m, 7H), 6.63 (s, 1H), 3.04 (br s, 8H), 1.69 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 148.9, 139.8, 135.1, 134.4, 130.7, 129.8, 129.6, 126.2, 122.3, 121.7, 108.8, 108.3, 79.6, 52.7, 45.9, 29.5; MS (ESI+) *m/z* calcd for $C_{22}H_{23}N_5O_3$ $[M + H]^+$ 406.18, found *m/z* 406.14.

Characterization of Compound 7{*4*}: 56% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.29 (s, 2H), 7.19 (s, 1H), 7.16 (s, 1H), 6.61 (s, 1H), 3.04 (s, 8H), 2.39 (s, 3H), 1.97 (s, 3H), 1.73 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 148.9, 138.6, 137.5, 134.0, 132.7, 131.4, 131.2, 128.3, 120.9, 120.8, 108.6, 108.4, 79.8, 52.6, 45.9, 29.9, 29.8, 21.0, 16.9; MS (ESI+) *m/z* calcd for $C_{24}H_{27}N_5O_3$ $[M + H]^+$ 434.21, found *m/z* 434.13.

General Procedures for Cbz-Deprotection of Alkyl-Substituted Benzopyranylpyrazoles 7{*5*}−7{*8*}. As a slight modification to the previously reported method,[17] Cbz-protected benzopyranylpyrazoles [**5**{*5*}−**5**{*8*}] were dissolved in anhydrous DCM (0.1 M), treated with dimethyl sulfide (27 equiv) and $BF_3 \cdot OEt_2$ (10 equiv), and stirred at room temperature for 1.5 h. After the addition of a second portion of dimethyl sulfide (22 equiv), the reaction was allowed to proceed for an additional 6 h at room temperature. The mixture was then poured into 10% aqueous NH_4OH (10 mL), and the aqueous layer was extracted with $CHCl_3$ three times. The combined organic layer was washed successively with ddH_2O and brine, dried over anhydrous Na_2SO_4, and condensed under reduced pressure to afford a crude mixture, which was purified by silica gel flash column chromatography.

Characterization of Compound 7{*5*}: 78% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.28 (s, 1H), 6.66 (s, 1H), 4.36 (t, J = 7.5 Hz, 2H), 3.02−3.14 (m, 8H), 1.95 (sextet, J = 7.5 Hz, 2H), 1.64 (s, 6H), 1.03 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 149.2, 135.0, 132.3, 129.7, 121.7, 121.4, 109.0, 108.8, 79.6, 53.4, 52.9, 46.0, 29.5, 24.6, 11.3; MS (ESI+) *m/z* calcd for $C_{19}H_{25}N_5O_3$ $[M + H]^+$ 372.43, found *m/z* 372.17.

Characterization of Compound 7{*6*}: 61% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.26 (s, 1H), 6.65 (s, 1H), 4.99−4.94 (m, 1H), 3.06 (m, 8H), 2.27−2.14 (m, 4H), 1.96−1.92 (m, 2H), 1.77−1.72 (m, 2H), 1.60 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 148.9, 135.0, 131.9, 129.8, 121.7, 121.6, 109.3, 109.0, 79.4, 61.8, 52.9, 46.0, 33.0, 29.2, 24.9; MS (ESI+) *m/z* calcd for $C_{21}H_{27}N_5O_3$ $[M + H]^+$ 398.21, found *m/z* 398.16.

Characterization of Compound 7{*7*}: 74% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.40 (s, 1H), 7.37−7.32 (m, 2H), 7.30−7.27 (m, 1H), 7.21 (d, J = 7.6 Hz, 2H), 6.62 (s, 1H), 5.62 (s, 2H), 3.15 (s, 8H), 1.65 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 148.8, 136.1, 135.0, 132.9, 130.2, 129.2, 128.2, 126.8, 122.2, 122.0, 109.1, 108.9, 79.7, 55.4, 51.7, 45.3, 29.5; MS (ESI+) *m/z* calcd for $C_{23}H_{25}N_5O_3$ $[M + H]^+$ 420.48, found *m/z* 420.14.

Characterization of Compound 7{*8*}: 64% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (ddd, J = 4.9, 1.6, 0.9 Hz, 1H), 8.27 (s, 1H), 7.63 (dt, J = 7.7, 1.7 Hz, 1H), 7.38 (s,

1H), 7.21 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 6.60 (s, 1H), 5.69 (s, 2H), 3.07 (s, 8H), 1.63 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 156.1, 150.0, 148.8, 137.4, 135.4, 133.3, 130.9, 123.2, 122.14, 122.09, 121.7, 108.9, 108.6, 79.5, 57.2, 52.3, 45.7, 29.4; MS (ESI+) m/z calcd for $C_{22}H_{24}N_6O_3$ $[M + H]^+$ 421.19, found m/z 421.13.

General Solution-Phase Parallel Reaction Procedures. Step A. Acid Coupling for 8{*1*,*a*}−8{*8*,*f*} (48 Compounds). Individual wells of a 96-deep-well filtration block were loaded with PS-HOBt (60 mg, loading level 1.1 g/mol). A solution of 6 different carboxylic acids (3.5 equiv), DIC (3.5 equiv), and DIPEA (3.5 equiv) in 1.2 mL of DMF was dispensed into the designated wells of the reaction block. The 96-deep-well reaction block was incubated at room temperature in a rotating oven [Robbins Scientific] for 3 h. The resins were then washed extensively with DMF and DCM sequentially (four times each), and Cbz-deprotected benzopyranylpyrazoles (**7**{*1*}−**7**{*8*}) (10 mg) in 1.2 mL of DCE were added to the activated ester on PS-HOBt resin. The reaction mixture was shaken at room temperature in a rotating oven for 15 h. The excess activated-ester-bound PS-HOBt resin was removed by filtration, and the filtrate was collected and condensed in vacuo using a GeneVac [Thermo Savant]. The crude products (**8**{*1*,*a*}−**8**{*8*,*f*}) were then analyzed by LC/MS without further purification as final members of the library.

Step B. Isocyanate and Isothiocyanate Coupling for 8{*1*,*g*}−8{*8*,*i*} (24 Compounds). A solution of either isocyanates or isothiocyanate (4 equiv, 0.095 mmol) in DCE (0.2 mL) was added to a designated well charged with Cbz-deprotected benzopyranylpyrazoles (**7**{*1*}−**7**{*8*}) (10 mg) in a 96-deep-well filtration block. The reaction block was incubated at room temperature for 15 h. After the completion of the reaction, PS-trisamine (10 equiv, 60 mg, loading level 4.36 mmol/g) was added as a scavenger resin to each well of the reaction block. The reaction block was then incubated at room temperature for an additional 15 h. PS-trisamine resin was removed by filtration, and the filtrate was collected and condensed in vacuo using a GeneVac [Thermo Savant]. The crude products (**8**{*1*,*g*}−**8**{*8*,*i*}) of each reaction were then analyzed by LC/MS without further purification as final members of the library.

Step C. Sulfonyl Chloride Coupling for 8{*1*,*j*}−8{*8*,*l*} (24 Compounds). A solution of sulfonyl chloride (4 equiv, 0.095 mmol) in Pyr/DCE (1:2 = v/v, 0.2 mL) was added to a designated well charged with Cbz-deprotected benzopyranylpyrazoles (**7**{*1*}−**7**{*8*}) (10 mg) in a 96-deep-well filtration block. The reaction block was incubated at 40 °C for 15 h. After the completion of the reaction, PS-trisamine (10 equiv., 60 mg, loading level: 4.36 mmol/g) was added as a scavenger to each well of the reaction block. The reaction block was then incubated at room temperature for an additional 15 h. PS-trisamine resin was removed by filtration, and the filtrate was collected and condensed in vacuo using a GeneVac [Thermo Savant]. The crude products (**8**{*1*,*i*}−**8**{*8*,*l*}) of each reaction were then analyzed by LC/MS without further purification as final members of the library.

General Procedures for Solid-Phase Parallel Synthesis. Step 1: Activation of Wang Resin. Individual wells of a 96-deep-well filtration block were loaded with Wang resins (20 mg, loading level 1.8 mmol/g). 4-Nitrophenylchloroformate (3 equiv) and DIPEA (3 equiv) in a cosolvent of DCE and THF (5:2, v/v) were added to the designated wells of the reaction block and incubated at room temperature in a rotating oven [Robbins Scientific, Inc.] for 5 h. The resulting resin **9** was extensively washed with DMF, MeOH, and DCM, sequentially (five times each) and dried in a vacuum desiccator.

Step 2: Benzopyranylpyrazole Substitution. The activated Wang resin **9** was incubated with benzopyranylpyrazole intermediate (**7**{*1*}−**7**{*8*}) (2 equiv) in DMF in a 96-deep-well filtration block. The reaction mixture was incubated at room temperature in a rotating oven [Robbins Scientific, Inc.] for 24 h, and the remaining unreacted *p*-nitrophenylcarbonate moiety on the resin was quenched with 20% piperidine in DMF for 3 h at room temperature. Then, benzopyranylpyrazole-loaded resin **10** was washed extensively with DMF, MeOH, and DCM sequentially and dried in a vacuum desiccator.

Step 3: Reduction of Nitro Group on Resin-Bound Benzopyranylpyrazoles. The nitro group of resin **10** was reduced to aniline by treatment with 2 M $SnCl_2 \cdot (H_2O)_2$ in DMF (1 mL) for 5 h at room temperature. The resulting resin **11** was washed extensively with DMF, MeOH, and DCM sequentially (five times each) and dried in a vacuum desiccator.

Step 4a: Acid Coupling for 12{*1*,*a*}−12{*8*,*f*} (48 Compounds). The activated ester was generated in situ by the activation of carboxylic acids (5 equiv) with PyBOP (5 equiv) and DMAP (2 equiv) in DMF with 3% *N*-methylmorpholine (NMM) for 15 min. Subsequently, the reaction cocktail was dispensed into the designated wells charged with resins **11**, and the reaction mixture was incubated in a rotating oven at room temperature for 24 h. The resins were then washed extensively with DMF, MeOH, and DCM and dried in a vacuum desiccator.

Step 4b: Isocyanate and Isothiocyanate coupling for 12{*1*,*g*}−12{*8*,*i*} (24 Compounds). A reaction cocktail of isocyanates or isothiocyanate (5 equiv) and anhydrous TEA (3 equiv) in anhydrous DCE was dispensed into the designated wells charged with resins **11**, and the reaction mixture was incubated in a rotating oven at room temperature for 24 h. The resins were then washed extensively with DMF, MeOH, and DCM sequentially, and dried in a vacuum desiccator.

Step 4c. Sulfonyl chloride coupling for 12{*1*,*j*}−12{*8*,*l*} (24 Compounds). A reaction cocktail of sulfonyl chloride (10 equiv) in anhydrous Pyr/DCE (1:2 = v/v) was dispensed into the designated wells charged with resins **11**, and the reaction mixture was incubated in a rotating oven at room temperature for 24 h. The resins were then washed with DMF, MeOH, and DCM sequentially and dried in a vacuum desiccator.

Step 5. Cleavage. After the resins in the 96 deep-well reaction blocks were dried under a high vacuum, the resins were treated with 50% TFA in DCM (0.7 mL/well) for 1 h

at room temperature. After removal of the resins by filtration, the filtrate was condensed under reduced pressure using a GeneVac [Thermo Savant]. The products were diluted with 50% H_2O/ACN and freeze-dried, which yielded a pale yellow powder. The purity of the final products was confirmed by LC/MS without further purification as final members of the library (**13**{*1*,*a*}−**13**{*8*,*l*}).

Representative Compounds of Benzopyranylpyrazole Library in Table 5. Characterization of Compound 8{*1*,*a*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.62 (s, 1H), 7.54 (s, 1H), 7.44−7.41 (m, 5H), 6.66 (s, 1H), 3.96−3.62 (m, 4H), 3.18−3.00 (m, 4H), 1.70 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 158.0, 148.5, 142.7, 135.7, 135.5, 130.7, 130.2, 128.8, 127.3, 127.1, 126.1, 123.6, 121.7, 109.6, 108.9, 79.8, 29.4; MS (ESI+) *m*/*z* calcd for $C_{30}H_{26}F_3N_5O_4$ [M + H]$^+$ 578.19, found *m*/*z* 578.16.

Characterization of Compound 8{*2*,*j*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.47 (s, 1H), 7.39 (dd, J = 9.0, 1.0 Hz, 2H), 7.05 (dd, J = 9.0, 1.0 Hz, 2H), 6.63 (s, 1H), 3.90 (s, 3H), 3.45−3.40 (m, 4H), 3.12−3.08 (m, 4H), 2.86 (s, 6H), 1.70 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 158.0, 148.2, 134.2, 132.7, 130.5, 127.7, 122.0, 121.5, 115.0, 109.6, 109.5, 79.9, 55.9, 51.7, 46.7, 38.6, 29.6; MS (ESI+) *m*/*z* calcd for $C_{25}H_{30}N_6O_6S$ [M + H]$^+$ 543.19, found *m*/*z* 543.14.

Characterization of Compound 8{*3*,*a*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59−7.54 (m, 3H), 7.53 (s, 1H), 7.51−7.47 (m, 3H), 7.45−7.40 (m, 5H), 6.64 (s, 1H), 3.99−3.58 (m, 4H), 3.22−2.95 (m, 4H), 1.71 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 158.0, 148.3, 139.9, 135.7, 134.5, 130.5, 130.1, 129.9, 129.8, 128.8, 127.3, 126.3, 122.5, 121.7, 109.4, 109.3, 79.9, 29.6; MS (ESI+) *m*/*z* calcd for $C_{29}H_{27}N_5O_4$ [M + H]$^+$ 510.21, found *m*/*z* 510.14.

Characterization of Compound 8{*4*,*a*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.44−7.40 (m, 5H), 7.29(s, 2H), 7.20 (s, 1H), 7.18 (s, 1H), 6.61 (s, 1H), 3.99−3.54 (m, 4H), 3.17−2.92 (m, 4H), 2.38 (s, 3H), 1.97 (s, 3H), 1.73 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 157.8, 148.3, 138.6, 137.6, 135.7, 134.1, 132.7, 131.5, 131.3, 130.8, 130.2, 128.8, 128.3, 127.3, 121.0, 120.9, 109.3, 109.2, 80.1, 29.9, 21.0, 16.9; MS (ESI+) *m*/*z* calcd for $C_{31}H_{31}N_5O_4$ [M + H]$^+$ 538.24, found *m*/*z* 538.15.

Characterization of Compound 8{*5*,*b*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.34−7.28 (m, 3H), 7.26−7.18 (m, 3H), 6.61 (s, 1H), 4.37 (t, J = 7.5 Hz, 2H), 3.87−3.81 (m, 2H), 3.63−3.57 (m, 2H), 3.11−3.05 (m, 2H), 3.02 (t, J = 7.8 Hz, 2H), 2.96−2.94 (m, 2H), 2.68 (t, J = 7.8 Hz, 2H), 1.96 (sextet, J = 7.4 Hz, 2H), 1.64 (s, 6H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 158.3, 148.5, 141.3, 135.3, 132.4, 129.4, 128.8, 128.7, 126.5, 121.8, 121.4, 109.7, 109.4, 79.9, 53.5, 51.4, 45.7, 35.3, 31.8, 29.5, 23.7, 11.3; MS (ESI+) *m*/*z* calcd for $C_{28}H_{33}N_5O_4$ [M + H]$^+$ 504.25, found *m*/*z* 504.20.

Characterization of Compound 8{*5*,*c*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.86 (d, J = 14.9 Hz, 1H), 7.34 (d, J = 4.9 Hz, 1H), 7.29 (s, 1H), 7.25(d, J = 3.7 Hz, 1H), 7.06 (dd, J = 5.1, 3.7 Hz, 1H), 6.70 (d, J = 14.9 Hz, 1H), 6.66 (s, 1H), 4.37 (t, J = 7.3 Hz, 2H), 3.94 (br s, 2H), 3.85 (br s, 2H), 3.20−3.13 (m, 4H), 1.96 (sextet, J = 7.5 Hz, 2H), 1.64 (s, 6H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 158.3, 148.5, 140.6, 136.4, 135.3, 132.4, 130.7, 129.4, 128.3, 127.7, 121.9, 121.4, 115.6, 109.7, 109.4, 79.9, 53.5, 29.5, 23.7, 11.3; MS (ESI+) *m*/*z* calcd for $C_{26}H_{29}N_5O_4S$ [M + H]$^+$ 508.19, found *m*/*z* 508.16.

Characterization of Compound 8{*6*,*j*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.30 (s, 1H), 6.68 (s, 1H), 5.01−4.96 (m, 1H), 3.50−3.46 (m, 4H), 3.19−3.14 (m, 4H), 2.88 (s, 6H), 2.30−2.16 (m, 4H), 2.00−1.94 (m, 2H), 1.81−1.73 (m, 2H), 1.63 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 148.3, 135.6, 131.9, 129.5, 122.0, 121.6, 110.5, 109.8, 79.8, 61.9, 51.7, 46.6, 38.6, 33.1, 29.3, 24.9; MS (ESI+) *m*/*z* calcd for $C_{23}H_{32}N_6O_5S$ [M + H]$^+$ 505.22, found *m*/*z* 505.14.

Characterization of Compound 8{*7*,*a*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.45−7.41 (m, 5H), 7.40 (s, 1H), 7.36 (t, J = 7.8 Hz, 2H), 7.29 (d, J = 7.3 Hz, 1H), 7.22 (d, J = 7.6 Hz, 2H), 6.61 (s, 1H), 5.62 (s, 2H), 4.04−3.55 (m, 4H), 3.21−2.89 (m, 4H), 1.66 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 158.2, 148.6, 136.2, 135.7, 132.9, 130.16, 130.15, 129.3, 128.8, 128.6, 128.3, 127.3, 126.9, 122.3, 122.1, 109.32, 109.28, 79.9, 55.5, 54.2, 42.4, 29.5; MS (ESI+) *m*/*z* calcd for $C_{30}H_{29}N_5O_4$ [M + H]$^+$ 524.22, found *m*/*z* 524.17.

Characterization of Compound 8{*8*,*h*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (dd, J = 4.9, 1.0 Hz, 1H), 8.32 (s, 1H), 7.65 (dt, J = 7.7, 2.0 Hz, 1H), 7.40 (s, 1H), 7.23 (dd, J = 7.5, 5.0 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 6.60 (s, 1H), 5.71 (s, 2H), 4.30 (d, J = 7.6 Hz, 1H), 3.69−3.62 (m, 1H), 3.56−3.46 (m, 4H), 3.13−3.03 (m, 4H), 2.00−1.93 (m, 2H), 1.76−1.68 (m, 3H), 1.65 (s, 6H), 1.40−1.30 (m, 2H), 1.17−1.07 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 157.1, 156.1, 150.0, 148.4, 137.4, 135.5, 133.3, 130.8, 123.2, 122.12, 122.10, 121.8, 108.9, 79.6, 57.2, 51.3, 49.7, 43.8, 34.2, 29.4, 25.9, 25.3; MS (ESI+) *m*/*z* calcd for $C_{29}H_{35}N_7O_4$ [M + H]$^+$ 546.28, found *m*/*z* 546.22.

Characterization of Compound 13{*3*,*a*}: ^{1}H NMR (500 MHz, CD_3OD) δ 7.84 (d, J = 7.3 Hz, 2H), 7.63−7.47 (m, 9H), 7.21 (s, 1H), 6.87 (s, 1H), 3.30−3.28 (m, 4H), 3.18−3.15 (m, 4H), 1.67 (s, 6H); MS (ESI+) *m*/*z* calcd for $C_{29}H_{29}N_5O_2$ [M + H]$^+$ 480.23, found *m*/*z* 480.15.

Characterization of Compound 13{*5*,*e*}: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (br s, 2H), 8.78 (br s, 1H), 7.82 (br s, 1H), 7.35 (s, 1H), 6.83 (s, 1H), 5.75 (s, 1H), 4.44 (t, J = 7.3 Hz, 2H), 3.42 (br s, 4H), 3.21−3.14 (m, 4H), 2.27 (s, 3H), 2.04−1.93 (m, 5H), 1.60 (s, 6H), 1.07 (t, J = 7.5 Hz, 3H); MS (ESI+) *m*/*z* calcd for $C_{24}H_{33}N_5O_2$ [M + H]$^+$ 424.26, found *m*/*z* 424.18.

Characterization of Compound 13{*6*,*c*}: ^{1}H NMR (500 MHz, CD_3OD) δ 8.53 (s, 1H), 7.87 (d, J = 15.2 Hz, 1H), 7.54 (d, J = 5.1 Hz, 1H), 7.39 (d, J = 3.4 Hz, 1H), 7.35 (s, 1H), 7.12 (dd, J = 4.9, 3.7 Hz, 1H), 6.89 (s, 1H), 6.79 (d, J = 15.4 Hz, 1H), 5.20−5.10 (m, 1H), 3.48−3.44 (m, 4H), 3.19−3.14 (m, 4H), 2.29−2.13 (m, 4H), 2.00−1.90 (m, 2H), 1.85−1.76 (m, 2H), 1.57 (s, 6H); MS (ESI+) *m*/*z* calcd for $C_{28}H_{33}N_5O_2S$ [M + H]$^+$ 504.24, found *m*/*z* 504.21.

Characterization of Compound 19{*8*,*b*}: ^{1}H NMR (500 MHz, CD_3OD) δ 8.69 (d, J = 4.9 Hz, 1H), 8.06 (dt, J =

7.8, 1.3 Hz, 1H), 7.99 (s, 1H), 7.59 (dd, $J = 6.9$, 6.1 Hz, 1H), 7.54 (s, 1H), 7.31−7.17 (m, 6H), 6.79 (s, 1H), 5.87 (s, 2H), 3.25−3.21 (m, 4H), 3.02 (t, $J = 7.2$ Hz, 2H), 2.95−2.91 (m, 4H), 2.75 (t, $J = 7.1$ Hz, 2H), 2.61 (t, $J = 7.7$ Hz, 1H), 1.63 (s, 6H); MS (ESI+) *m*/*z* calcd for $C_{31}H_{34}N_6O_2$ $[M + H]^+$ 523.27, found *m*/*z* 523.32.

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Supporting Information Available. Experimental procedures, complete characterization (^{1}H NMR, gCOSY, LC/MS, and NOESY) to confirm the regioselectivity of compounds **5**{*1*}−**5**{*10*}, a detailed procedure of the chemoinformatic analysis with principal component analysis data, copies of NMR and LC/MS spectra (PDA detector) for the representative library members without further purification, ^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, **3**, **4**, **7**{*1*}−**7**{*8*}, and LC/MS analysis data of library members. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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