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Synthesis of Molecular Frameworks Containing Two Distinct Heterocycles Connected in a Single Molecule with Enhanced Three-Dimensional Shape Diversity

Donghyun Lim[a] and Seung Bum Park*[a, b]

Abstract: Herein, we report the synthesis of fused-triazole scaffolds that are connected by pyrimidines, pyrazoles, or pyrazolopyrimidines through carbohydrate-derived stereodivergent linkers. Pyrimidine-, pyrazole-, or pyrazolopyrimidine-based carbohybrids were constructed through condensations of the key intermediates, 2-*C*-formyl glycals, with various dinucleophiles. Fused-triazole scaffolds were obtained through intramolecular 1,3-dipolar cycloadditions after selective functionalization of the carbohybrid polyol moieties with azide and alkyne functionalities using S_N2-type alkylations or Mitsunobu reactions. Overall, this synthetic method affords two distinct privileged substructures in a single molecule, connected by stereodivergent diol linkers derived from abundant natural chiral sources, namely, carbohydrates. The resulting vicinal diols in the linker were further modified to achieve unique connectivities between the two privileged structures for maximized three-dimensional shape diversity, which we called the linker diversification strategy.

Keywords: carbohydrates · cycloaddition · fused-ring systems · molecular diversity · privileged structures

Introduction

One of the greatest challenges in the field of chemical biology is the identification of new small-molecule modulators that can selectively perturb the function of gene products.[1] Such chemical modulators can serve as specific bioprobes for the mechanistic studies of mysterious biological systems at the molecular level, which is the main concept of chemical genetics.[2] In addition, these small-molecule modulators can open new doors for the development of new therapeutic agents with unique modes of action.[3] The discovery of new bioactive small molecules has been achieved by means of high-throughput screening (HTS) against various biological targets, which can be classified into two major approaches: target-based enzymatic assays and discovery-driven phenotypic assays.[4] Recently, the screening paradigm has shifted toward phenotypic screening as the dominant strategy for discovering new first-in-class therapeutics.[5] Therefore, image-based high-content screening (HCS) has received increased attention in the pharmaceutical industry and academia to expand the repertoire of "druggable" targets.[6]

Regardless of the type of HTS, the successful discovery of new small-molecule modulators has been significantly influenced by the molecular diversity of small-molecule screening libraries.[7] Therefore, it is essential to efficiently construct a collection of druglike small molecules with maximum molecular diversity. To this end, synthetic chemists have adopted a diversity-oriented synthesis (DOS) approach that aims at the efficient generation of complex and druglike compound libraries that contain large numbers of structurally diverse molecular frameworks.[8] We have been particularly interested in the development of divergent and robust synthetic pathways for the efficient construction of a druglike small-molecule library[9] through the creative assembly of polyheterocycles embedded with privileged substructures including benzopyrans,[9a] benzodiazepines,[9b] acetal-fused pyranopyrones,[9c] and tetrahydroindazolones.[9d] We named this approach privileged-substructure-based diversity-oriented synthesis (pDOS).[10] It is worth mentioning that our new polyheterocycles embedded with privileged substructures showed enhanced selectivities and high relevance in multiple biological assays, which was confirmed by the successful identification of specific small-molecule modulators for various biological targets, including anticancer, antiosteoporosis, and antidiabetic agents.[11]

Among the synthetic pathways we developed, we have pursued the further elaboration of a particular molecular framework, namely, carbohybrids. These are defined as acyclic polyols fused with various privileged heterocycles, which are widely dispersed in nature and have interesting biological activities (Figure 1). For example, bengazoles are antifungal marine natural products that contain a unique

[a] D. Lim, Prof. Dr. S. B. Park
Department of Biophysics and
Chemical Biology/Bio-MAX Institute
Seoul National University
Seoul, 151-747 (Korea)
Fax: (+82) 2-884-4025
E-mail: sbpark@snu.ac.kr

[b] Prof. Dr. S. B. Park
Department of Chemistry
Seoul National University
Seoul, 151-747 (Korea)

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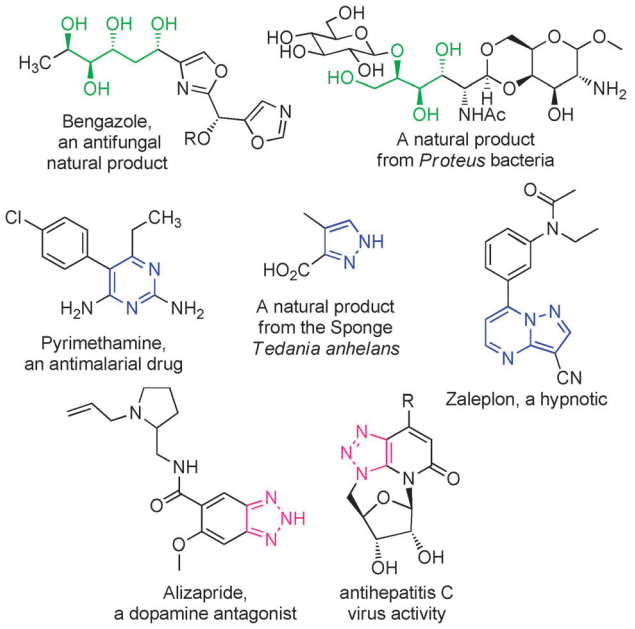


Figure 1. Bioactive small molecules containing carbohybrid (green), pyrimidine, pyrazole, pyrazolopyrimidine (blue), and triazole (pink) substructures.

bisoxazole moiety connected to a carbohydrate-like acyclic polyol.[12] Many iminoalditols with acyclic polyol chains have been identified as inhibitors of glycosyltransferases and glycosidases for diverse therapeutic applications.[13] Sialic acid and its derivatives are polyol-fused heterocyclic molecules widely distributed in nature.[14] On the basis of these interesting structural motifs, we developed an efficient one-pot protocol for the synthesis of acyclo-*C*-nucleosides as carbohybrids starting from 2-*C*-formyl glycals.[15] Our synthetic method overcame the limitations of previously reported protocols that used 2-*C*-formyl glycals, such as poor yields and the use of strong base. With this powerful method in hand, we envisioned the further expansion of our carbohybrid collection through the creation of new molecular frameworks through the incorporation of various diversity elements, including skeletal, stereochemical, and substituent diversity. In fact, a new type of carbohybrid, elaborated through the modification of a glycosidic linkage at the polyol moiety, has been identified in *Proteus* bacteria (Figure 1, green highlights).[16]

Herein, we report a systematic modification of carbohybrid collections to create new molecular frameworks that contain two distinct privileged substructures in a single molecule. Acyclic polyols fused with pyrimidines, pyrazoles, or pyrazolopyrimidines served as primary carbohybrid skeletons; such heterocycles are privileged substructures frequently observed in bioactive natural products and pharmaceutical agents (Figure 1, blue highlights).[17] We also identified 1,2,3-triazoles fused with diverse heterocycles as modification elements for our carbohybrids because they are abundant in many bioactive compounds. In fact, there are only a half dozen reports on the synthesis of a fused 1,2,3-triazole-based compound library, and the strategies for their preparation are still in the early stages of development.[18] As shown in Figure 2, our carbohybrid-derived new molecular

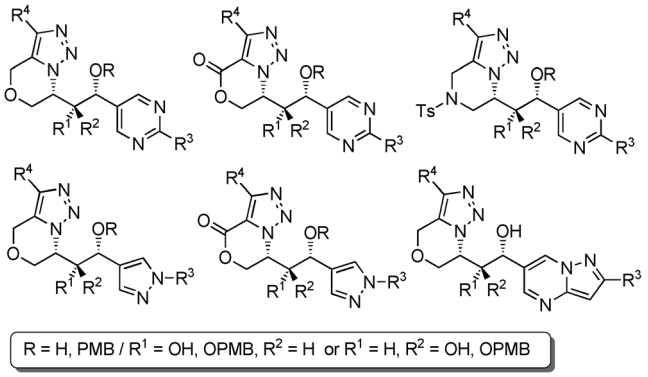


Figure 2. New molecular frameworks containing two distinct privileged structures connected with stereodivergent linkers. PMB denotes the *p*-methoxybenzyl protecting group.

frameworks contain two privileged substructures connected with stereodivergent vicinal diols. Our synthetic scheme was designed to construct fused triazoles through the intramolecular 1,3-dipolar cycloaddition of azido and alkyne functionalities, which can be installed at the desired positions of the polyol moiety. The intramolecular cycloaddition reaction is quite an efficient transformation and is tolerant of a broad range of substrates.

Next, we aimed to modify the stereodivergent vicinal diol functionality in the linker with various chemical reactions, which would provide new kinds of skeletal diversity through the creation of additional molecular scaffolds. The various tetherings of the chirally enriched vicinal diols allowed the specific display of the two privileged heterocycles in a diverse three-dimensional (3D) space owing to the conformational restriction of the rotatable bonds in the linker region. In this manuscript, we describe in detail our stereodivergent synthetic strategy to control the spatial orientation of privileged heterocycles using carbohybrid molecular frameworks.

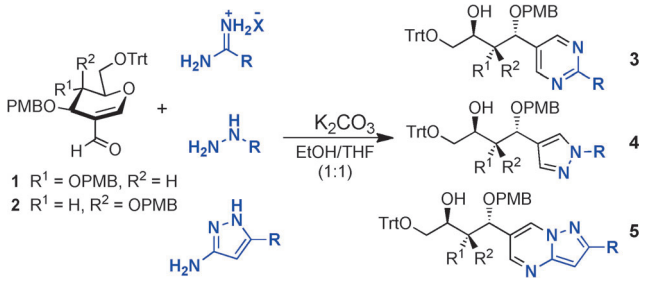
Results and Discussion

Preparation of pyrimidine- and pyrazole-based carbohybrids: We recently reported the efficient one-pot synthesis of pyrimidine-, pyrazole-, and pyrazolopyrimidine-based carbohybrids from 2-*C*-formyl glycals.[15] In this study, we sought to diversify the polyheterocyclic skeletons through the introduction of fused triazoles in these carbohybrids. Hence, we prepared the key intermediates **1** and **2** through the selective protection of hydroxyl groups on D-glucal and D-galactal, and a subsequent Vilsmeier–Haack formylation. In brief, the primary hydroxyl group at the C-6 position was protected with a trityl group, and two of the secondary hydroxyl groups were orthogonally protected with *p*-methoxybenzyl (PMB) groups (see the Supporting Information).

After formylation in the presence of $POCl_3$ in dimethylformamide (DMF), the intermediates **1** and **2** were transformed into acyclic polyol-fused pyrimidines **3**, pyrazoles **4**, and pyrazolopyrimidines **5** through the imine formation with dinucleophiles followed by nucleophilic sugar-ring opening.

As shown in Table 1, this transformation preserved its broad scope of substrate generality and afforded various polyheterocycles in moderate to good yields. The dinucleophilic condensation of 2-*C*-formyl D-glucal **1** along with ring opening gave almost an identical result to that of 2-*C*-formyl D-galactal **2** in terms of yield and the reaction time under the same conditions (Table 1, entries 1 and 2). In our previous reports, we clearly demonstrated that both 2-*C*-formyl D-glucal and 2-*C*-formyl D-galactal were coupled with various dinucleophiles in a similar pattern (see the Supporting Information).[15] Therefore, in this report we focused on the formation of fused triazoles and the subsequent diversification in spatial orientation of privileged heterocycles using galactal-based carbohybrids (Table 1, entries 2–8). When substituted guanidines and benzamidines were used in a salt form, we generated the free bases of dinucleophiles in the presence of K_2CO_3, which afforded the polyol-fused pyrimidines **3a–d** in moderate to respectable yields (Table 1, entries 1–4). Synthesis of the pyrazole-based carbohybrid **4a** was successfully achieved in excellent yields by means of the cyclocondensation with methylhydrazine under the basic co-solvent conditions at room temperature (Table 1, entry 5). In the case of phenylhydrazine, the desired product **4b** was not observed under identical conditions, probably owing to the inherently poor nucleophilicity of arylhydrazines. However, thermal activation at 80 °C allowed the formation of the desired product **4b** in modest yield (Table 1, entry 6). In the case of 5-substituted 3-aminopyrazoles, the conventional heating at 80 °C was also required to obtain the desired pyrazolopyrimidines **5a**,**b** in moderate to good yields (Table 1, entries 7 and 8). As observed in the arylhydrazine cases, the presence of a phenyl substituent at the C-5 position of 3-aminopyrazole lowered its reactivity and caused a significant reduction in yield.

Table 1. Synthesis of pyrimidine-, pyrazole-, and pyrazolopyrimidine-based carbohybrids.

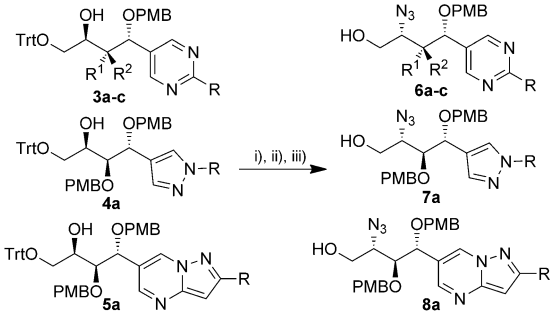


Entry	R^1	R^2	R	Conditions	Yield [%]	Product
1	OPMB	H	NMe_2	RT, 16 h	85	**3a**
2	H	OPMB	NMe_2	RT, 16 h	80	**3b**
3	H	OPMB	*p*-chloro-phenyl	RT, 21 h	52	**3c**
4	H	OPMB	NH_2	80 °C, 21 h	68	**3d**
5	H	OPMB	methyl	RT, 14 h	94	**4a**
6	H	OPMB	phenyl	80 °C, 12 h	55	**4b**
7	H	OPMB	methyl	80 °C, 11 h	70	**5a**
8	H	OPMB	phenyl	80 °C, 12 h	44	**5b**

Construction of fused triazoles through intramolecular 1,3-dipolar cycloadditions: There are many reports on privileged structures as core skeletons for the synthesis of potentially bioactive small molecules and as key binding motifs for various biopolymers, especially enzymes and proteins.[19] We previously proposed pDOS[10] as an efficient strategy for the construction of new polyheterocyclic molecular frameworks that contain privileged substructures to systematically perturb various biological processes, including protein–protein interactions (PPIs). Along this line, we envisioned that the linking of two privileged substructures in a single hybrid molecule might be a powerful strategy to modulate potential PPIs. Each privileged substructure in these hybrid molecules can serve as a binding motif for different PPI partners, which could increase the possibility of perturbing a specific protein–protein interaction in the complex signaling networks.

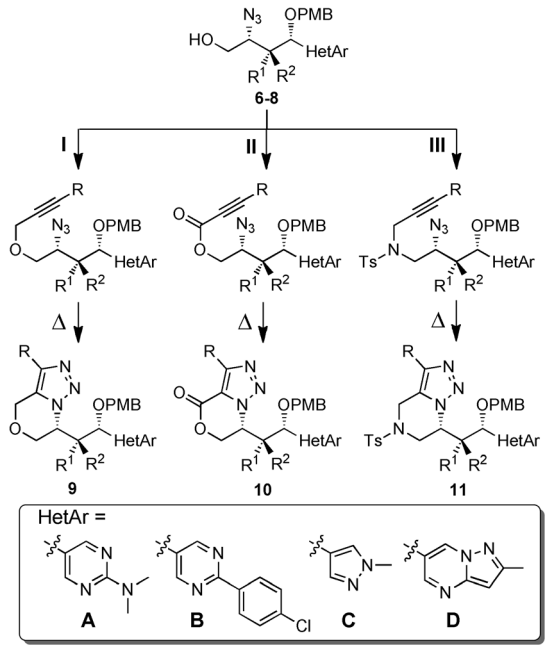
With our robust and general transformation of key intermediates **1** and **2** with various dinucleophiles, including substituted guanidines, benzamidines, hydrazines, and 3-aminopyrazoles, we pursued the further modification of our resulting carbohybrids. The construction of new core skeletons through the connection of two distinct privileged substructures in a single molecule using various linkers has never been explored in the fields of molecular diversity and diversity-oriented synthesis. Inspired by their abundance in many bioactive compounds[18b,d] and the early developmental stage of druglike fused 1,2,3-triazole libraries,[18a,c–f] we designed the strategic linkage of fused 1,2,3-triazoles at the other ends of acyclic *C*-nucleosides **3–5** (Figure 2).

As shown in Scheme 1, the free secondary hydroxyl groups in **3–5**, generated by the cyclocondensations with dinucleophiles, were mesylated, and the trityl-protected pri-



Scheme 1. Synthesis of intermediates (**6–8**) that harbor β-azido hydroxyl functionality. i) MsCl, TEA, CH_2Cl_2, 0 °C–RT; ii) *p*-TsOH, MeOH, RT; iii) NaN_3, DMF, 100 °C. **3a**, **6a**: R = NMe_2, R^1 = OPMB, R^2 = H, 62 %; **3b**, **6b**: R = NMe_2, R^1 = H, R^2 = OPMB, 88 %; **3c**, **6c**: R = *p*-chlorophenyl, R^1 = H, R^2 = OPMB, 73 %; **4a**, **7a**: R = Me, 67 %; **5a**, **8a**: R = Me, 75 %.

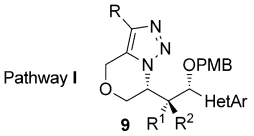
mary alcohol was unmasked in the presence of *p*-toluenesulfonic acid in methanol. Then, nucleophilic substitution of the *O*-mesyl group with NaN_3 in DMF afforded intermediates **6–8** that bore β-azido hydroxyl functionality in excellent three-step yields. Owing to the mild reaction conditions, no deterioration of chiral enrichment was observed, which might have been caused by the epoxide-associated epimerization through neighboring-group participation (see the Supporting Information). For the formation of the fused triazoles, alkyne functionality was then introduced by the reactions of the hydroxyl groups in **6–8** with various alkyne building blocks. As shown in Scheme 2, the nucleophilic substitution of various alkynyl halides with the β-azido hydroxyl moiety in the presence of NaH afforded the corresponding ether intermediates, which underwent the intramolecular 1,3-dipolar cycloadditions in toluene heated to reflux without further purification to yield the desired morpholine-fused triazoles **9** in moderate to excellent yields (Scheme 2, pathway I). The hydroxyl moieties in **6–8** were also converted to ester linkages through Mitsunobu reactions with alkynyl acids, and the subsequent intramolecular 1,3-dipolar cycloadditions yielded 2-morpholine-fused triazoles **10** in excellent yields (Scheme 2, pathway II). Alkynyl sulfonamides were successfully introduced under Mitsunobu conditions, and the subsequent intramolecular cycloaddition in toluene heated to reflux afforded piperazine-fused triazoles **11** in high yields (Scheme 2, pathway III). Unlike Huisgen cycloaddition, these intramolecular 1,3-dipolar cycloadditions selectively formed single 1,5-regioisomers without copper catalyst, regardless of alkynyl substituents due to the restricted geometries. However, it is worth mentioning that the cycloaddition reaction rate was much slower in the case of the ester intermediates (Scheme 2, pathway II) than the other substrates under conventional reflux conditions. Instead, microwave irradiation in DMF for 3 min at 150 W and 120 °C was sufficient to convert all the ester intermediates to the desired 1,2,3-triazoles in good yields.



Scheme 2. Synthesis of fused 1,2,3-triazoles. I) Haloalkynes, NaH, DMF (S_N2-type O-alkylation), then heating in toluene at reflux. II) Alkynyl acids, diisopropyl azodicarboxylate (DIAD), PPh_3, THF (Mitsunobu reaction), then microwave irradiation, 150 W, 120 °C, DMF. III) Alkynyl sulfonamides, DIAD, PPh_3, THF (Mitsunobu reaction), then heating in toluene at reflux.

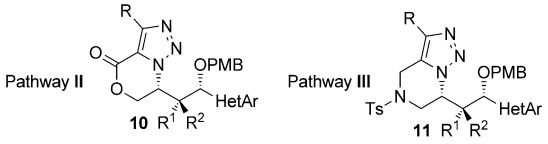
As shown in Tables 2 and 3, we successfully achieved the efficient synthesis of new chimera compounds (**9–11**) that contained various fused triazoles and privileged heterocycles

Table 2. New molecular frameworks containing two distinct privileged substructures in a single hybrid molecule obtained through pathway I.



Entry	HetAr	R^1	R^2	R	Yield [%]	Product
1	**A**	OPMB	H	hydrogen	65	**9a**
2	**A**	OPMB	H	methyl	89	**9b**
3	**A**	OPMB	H	ethyl	90	**9c**
4	**A**	OPMB	H	phenyl	65	**9d**
5	**A**	OPMB	H	3-methoxyphenyl	73	**9e**
6	**A**	OPMB	H	1-naphthalene	67	**9f**
7	**A**	H	OPMB	hydrogen	78	**9g**
8	**A**	H	OPMB	methyl	80	**9h**
9	**A**	H	OPMB	ethyl	89	**9i**
10	**A**	H	OPMB	phenyl	64	**9j**
11	**A**	H	OPMB	4-fluorophenyl	58	**9k**
12	**A**	H	OPMB	4-methoxyphenyl	84	**9l**
13	**A**	H	OPMB	2-thienyl	42	**9m**
14	**B**	H	OPMB	methyl	77	**9n**
15	**C**	H	OPMB	methyl	60	**9o**
16	**D**	H	OPMB	methyl	88	**9p**

Table 3. New molecular frameworks containing two distinct privileged structures in a single hybrid molecule obtained through pathways II and III.

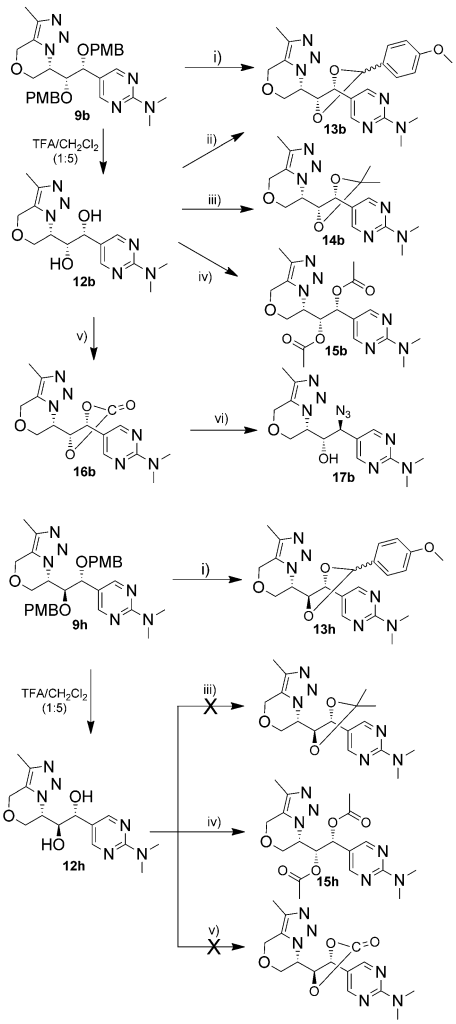


Entry	Path	HetAr	R^1	R^2	R	Yield [%]	Product
1	II	**A**	OPMB	H	methyl	95	**10a**
2	II	**A**	H	OPMB	methyl	72	**10b**
3	II	**B**	H	OPMB	methyl	92	**10c**
4	II	**B**	H	OPMB	ethyl	90	**10d**
5	II	**C**	H	OPMB	methyl	73	**10e**
6	II	**C**	H	OPMB	phenyl	77	**10f**
7	III	**A**	OPMB	H	hydrogen	58	**11a**
8	III	**A**	OPMB	H	phenyl	73	**11b**
9	III	**A**	OPMB	H	4-methyl-phenyl	70	**11c**
10	III	**A**	OPMB	H	4-cyano-phenyl	71	**11d**

connected with chirally enriched vicinal diols. This synthetic route is modular enough to construct any combination of fused 1,2,3-triazoles with privileged polyheterocycles, which dramatically enhances the expandability of their molecular diversity. In addition, we can envision the access to all possible diastereomers of final compounds by using different starting D- and L-hexoses.

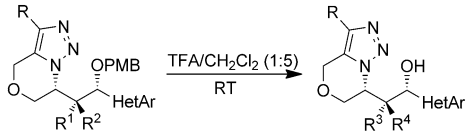
Modification of the linker to maximize skeletal diversity in 3D space: After the successful construction of new chimera compounds that contained fused 1,2,3-triazoles and privileged heterocycles connected with chirally enriched vicinal diols, we pursued the introduction of a new diversity element. This was to be achieved through molecular-shape transformation by using various chemical reactions of the stereodivergent vicinal diols in the linker. In fact, the actual arrangement of privileged substructures in 3D space might be critical to potential interactions with biopolymers.[20] By interlocking vicinal diols in the linkers of our chimera compounds, the projection of two privileged structures could be dramatically changed, and the potential interaction of these unique skeletons to biopolymers can be quite specific due to their limited conformational freedom with a prepaid entropic penalty. The generation of molecular-shape diversity might lead to the diversification of biological activity, with a similar set of appendages in a complementary 3D fashion. To this end, the PMB protecting groups were removed in the presence of 20% trifluoroacetic acid in dichloromethane to release free vicinal diols in excellent yields (Table 4).

As shown in Scheme 3, the resulting vicinal diols were modified through various chemical transformations to uniquely position the two privileged substructures in 3D space. For example, the acetal exchange reaction of the glucal-derived (*R*,*R*)-vicinal diol **12b** with *p*-anisaldehyde dimethyl acetal afforded the chimera compound **13b** that contained *p*-methoxyphenyl acetal as a 71:29 diastereomeric mixture as determined by ^{1}H NMR spectroscopy. Interestingly, **13b** can also be obtained by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) treatment of PMB-protected **9b** in anhydrous CH_2Cl_2 with a similar 81:19 diastereomeric ratio. When the galactal-derived (*R*,*S*)-vicinal diol compound **9h** with PMB protecting groups was treated with DDQ, a different *p*-methoxyphenyl acetal-containing chimera compound **13h** was obtained, with a diastereomeric ratio of 66:34. The glucal-derived (*R*,*R*)-vicinal diol **12b** was tolerant of various



Scheme 3. Modification of the linker to maximize skeletal diversity in 3D space. i) DDQ, CH_2Cl_2, 0 °C–RT; **13b**, 59% d.r. = 81:19; **13h**, 33%, d.r. = 66:34. ii) Anisaldehyde dimethyl acetal, *p*-TsOH, CH_2Cl_2, RT; **13b**, 55%, d.r. = 71:29. iii) 2,2-Dimethoxypropane, *p*-TsOH, acetone, RT; **14b**, 85%. iv) Acetic anhydride, TEA, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, RT; **15b**, 95%; **15h**, 89%. v) CDI, CH_2Cl_2, RT; **16b**, 79%. vi) NaN_3, H_2O, DMF, 110 °C; **17b**, 49%.

Table 4. Deprotection of PMB groups in the linker.



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Entry	SM	HetAr	R^1	R^2	R^3	R^4	R	Yield [%]	Product
1	**9a**	**A**	OPMB	H	OH	H	hydrogen	99	**12a**
2	**9b**	**A**	OPMB	H	OH	H	methyl	92	**12b**
3	**9c**	**A**	OPMB	H	OH	H	ethyl	92	**12c**
4	**9g**	**A**	H	OPMB	H	OH	hydrogen	99	**12g**
5	**9h**	**A**	H	OPMB	H	OH	methyl	88	**12h**
6	**9i**	**A**	H	OPMB	H	OH	ethyl	99	**12i**
7	**9j**	**A**	H	OPMB	H	OH	phenyl	96	**12j**
8	**9k**	**A**	H	OPMB	H	OH	4-fluorophenyl	96	**12k**
9	**9l**	**A**	H	OPMB	H	OH	4-methoxyphenyl	89	**12l**
10	**9m**	**A**	H	OPMB	H	OH	2-thienyl	76	**12m**
11	**9n**	**B**	H	OPMB	H	OH	methyl	94	**12n**
12	**9o**	**C**	H	OPMB	H	OH	methyl	99	**12o**

diol-based chemical transformations. For example, the acid-catalyzed acetal exchange reaction of **12b** with 2,2-dimethoxypropane provided dimethyl acetal **14b** in high yield, and the treatment of **12b** with 1,1-carbonyldiimidazole (CDI) in CH_2Cl_2 allowed the formation of carbonate **16b** in good yield. However, the galactal-derived (*R*,*S*)-vicinal diol **12h** did not undergo the ring-forming exchange reaction to the dimethyl acetal under identical conditions (Scheme 3, route iii), possibly due to $A_{1,2}$-strain-like repulsion between two privileged heterocycles upon acetal-based cyclization of the vicinal diol. Similarly, the carbonate compound synthesized by the treatment of **12h** with CDI was transiently generated, but readily decomposed back to the starting compound **12h** at room temperature, which demonstrated the instability of the tethered five-membered ring system from galactal-derived (*R*,*S*)-vicinal diols (see Figure 3c).

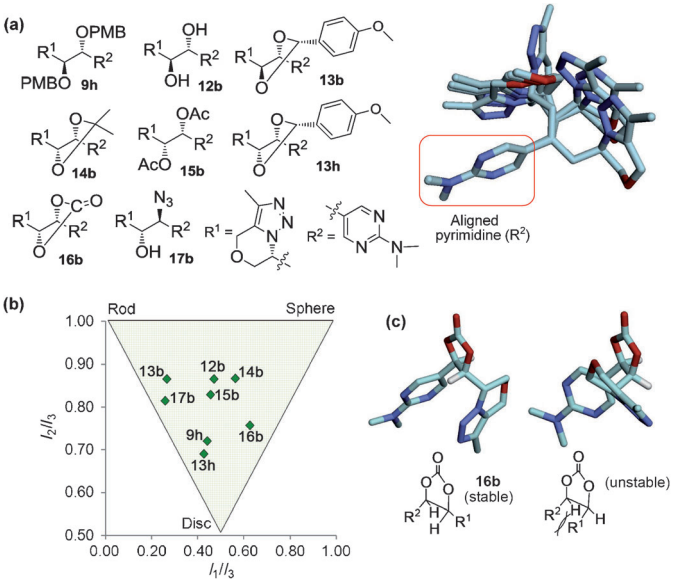

Figure 3. a) Overlay of eight representative molecules. Energy-minimized conformers were aligned with respect to the pyrimidine moiety. Branching linker atoms are not shown in this figure for clarity. b) PMI plot depicting the eight representative compounds. c) The structural differences in energy-minimized conformers of glucal-derived (*R*,*R*)-carbonate **16b** and unstable galactal-derived (*R*,*S*)-carbonate.

The further diversification of stereodivergent vicinal diols was carried out through nucleophilic ring opening of the cyclic carbonate **16b** with NaN_3 to yield the monohydroxy-azido compound **17b**.[21] To maximize the molecular-shape diversity of our compound collections, the stereodivergent vicinal diols were modified with acetylation to provide **15b** and **15h** as a linear version of our chimera compounds.

Overall, the vicinal diol modifications introduced new skeletal diversity in our compound collection: two heterocyclic substructures could be uniquely oriented in 3D space through the tethering process of vicinal diols. To visualize the shape diversity we achieved, we selected eight representative chimera compounds (**9h**, **12b**, **13b**, **13h**, **14b**, **15b**, **16b**, and **17b**) with identical appendages that differed with respect to stereochemistry and/or tethering moiety of vicinal diols. The eight compounds were virtually modeled in 3D space, and their energy-minimized molecular structures were superimposed and aligned with respect to the pyrimidine group. As shown in Figure 3a, the orientations of morpholine-fused triazoles diverged significantly in 3D space through the rigidified linker regions, which emphasized the importance of the shape diversity in our chimera compounds and the associated spacial display of two privileged substructures within a single molecule. Moreover, to quantify the discrete shape differences of eight representative compounds in 3D space, we performed the normalized principal moments of inertia (PMI) analysis.[22] The PMI analysis has been used to capture the shape-based distribution of the small molecule library. The points in the resulting plot occupy an isosceles triangle defined by the vertices (0,1), (0.5,0.5), and (1,1), which correspond to the shape of a rod, disc, and sphere, respectively. As shown in Figure 3b, our representative compounds were dispersed in the PMI plot, which indicates that our linker-diversification strategy of stereodivergent vicinal diols allows access to different chemical spaces by means of the unique display of two privileged substructures in 3D space.

The differences in the stereochemistry and linker tethering lead to the significant shape and skeletal diversity of final compounds, thus emphasizing the importance of the unique design of molecular frameworks and their connectivity. It is worth mentioning that the overall shape of a small molecule is the most fundamental element that influences its specific modulation of biological functions and signaling pathways. Indeed, a substantial "shape space" coverage (in other words, molecular-shape diversity) has been correlated with a broad range of perturbations in biological activities.[22] In this study, we demonstrated that the shape space coverage of chimera carbohybrids that contain two unique privileged substructures could be expanded through the tethering of the stereodivergent vicinal diols in the linker region. Therefore, in the field of diversity-oriented synthesis, our linker-diversification strategy affords a new way to access molecular-shape diversity in 3D space and a new tool to expand this molecular diversity without significant changes in substituents.

Conclusion

New molecular frameworks were developed through the systematic incorporation of two distinct privileged substructures in a single molecule. As substituents of carbohybrids, pyrimidines, pyrazoles, and pyrazolopyrimidines were synthesized by means of the condensations of common intermediates, 2-*C*-formyl glycals, with the corresponding dinucleophiles in simple one-pot procedures. To enhance the biological relevance of these compounds, particularly with respect to the potential perturbations of protein–protein interactions, privileged fused triazoles were introduced at the

other end of the resulting carbohybrids. The β-azido hydroxyl moieties in the key intermediates were prepared by selective polyol modifications, and the primary hydroxyl groups were modified with various alkyne building blocks. The resulting intermediates, which contain both azido and alkyne functionalities, were then subjected to intramolecular copper-free 1,3-dipolar cycloaddition by conventional heating or microwave irradiation to efficiently yield the fused 1,2,3-triazoles as a single 1,5-regioisomer. The key feature of these carbohybrids was the connection of two privileged heterocycles with a stereochemically enriched vicinal diol linker, which was further utilized for the expansion of molecular-shape diversity through tethering of the stereodivergent vicinal diols using various chemical reactions. This allowed the unique orientation of privileged substructures in 3D space. This linker-diversification strategy offers a new diversity element through molecular-shape transformation without substituent changes. PMI analysis and the structure alignment of energy-minimized representative compounds clearly demonstrated the importance of stereochemistry and linker-modification chemistry of vicinal diols. The molecular recognition of bioactive small molecules by biopolymers is significantly influenced by their 3D conformations.[23] Therefore, the linker-diversification strategy and our new molecular frameworks can provide a valuable platform on which to build molecular diversity in 3D space, ultimately leading to the identification of specific bioactive small molecules, particularly protein–protein interaction modulators.

Experimental Section

General: All commercially available reagents and solvents were used without further purification unless noted otherwise. All the solvents were purchased form commercial venders. ^{1}H and ^{13}C NMR spectra were obtained using Bruker DRX-300 (Bruker Biospin, Germany), Agilent 400-MR DD2 (Agilent, USA), or Varian Inova-500 (Varian Assoc., Palo Alto, USA) instruments. Chemical shifts were reported in ppm from tetramethylsilane (TMS) as internal standard or the residual solvent peak ($CDCl_3$; ^{1}H: $\delta=7.26$ ppm; ^{13}C: $\delta=77.23$ ppm). Multiplicity was 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), brs (broad singlet), and so on. Coupling constants are reported in hertz. Mass spectrometric analysis was performed using a Finnigan Surveyor MSQ Plus LC/MS (Thermo) with electrospray ionization (ESI). Microwave reaction was performed using a CEM Discover Benchmate microwave synthesizer. The conversion of starting materials was monitored by thin-layer chromatography (TLC) using precoated glass-backed plates (silica gel 60; $F_{254}=0.25$ mm), and the reaction components were visualized by observation under UV light (254 and 365 nm) or by treatment of TLC plates with visualizing agents such as $KMnO_4$, phosphomolybdic acid, ceric sulfate, and ninhydrin followed by heating. Products were purified by flash column chromatography on silica gel (230–400 mesh) using a mixture of EtOAc/hexane or MeOH/CH_2Cl_2 as eluents. The energy-minimized structures of molecules were obtained by V_{conf} Interface v2.0 using default parameters and visualized by Discovery Studio 3.0. The principal moment of inertia (PMI) of the energy-minimized structures was calculated using PreADMET v2.0 and visualized by a PMI plot as described previously.[22a]

General procedure for the preparation of pyrimidine-, pyrazole-, and pyrazolopyrimidine-based carbohybrids 3–5: A solution of 2-*C*-formyl glycal **1** or **2** (100 mg) in THF (3 mL) was added to a stirred solution of dinucleophile (2 equiv) and K_2CO_3 (5 equiv) in ethanol (3 mL). The reaction mixture was stirred at room temperature or 80 °C until the full conversion of starting materials monitored by TLC. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layer was dried over anhydrous Na_2SO_4. The filtrate was condensed under reduced pressure and subjected to flash column chromatography. Carbohybrid **3b**: Prepared from **2** and 1,1-dimethylguanidine sulfate salt, amorphous white solid. Yield: 80%; $[\alpha]_D^{25}=-9.69$ ($c=0.91$, $CHCl_3$); $R_f=0.17$ (EtOAc/hexane 1:2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.24$ (s, 2H), 7.42 (d, $J=8.1$ Hz, 6H), 7.30–7.22 (m, 9H), 7.15 (d, $J=8.6$ Hz, 2H), 6.82–6.78 (m, 4H), 6.69 (d, $J=8.3$ Hz, 2H), 4.40 (d, $J=11.2$ Hz, 1H), 4.24 (d, $J=7.6$ Hz, 1H), 4.18 (d, $J=11.2$ Hz, 1H), 4.11–4.05 (m, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.73 (dd, $J=7.6$, 2.4 Hz, 1H), 3.27 (dd, $J=9.3$, 6.1 Hz, 1H), 3.21 (s, 6H), 3.08 (dd, $J=9.3$, 6.4 Hz, 1H), 2.39 ppm (d, $J=7.6$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=162.4$, 159.5, 159.4, 157.9, 144.1, 130.2, 129.8, 129.7, 128.9, 128.0, 127.2, 119.1, 114.0, 113.8, 86.9, 81.0, 76.5, 74.3, 70.3, 70.0, 64.7, 60.6, 55.5, 37.4, 14.4 ppm; HRMS (FAB+): m/z calcd for $C_{45}H_{47}N_3O_6$ $[M+H]^+$: 726.3543; found: 726.3536.

General procedure for the preparation of key intermediates 6–8 that harbor β-azido hydroxyl functionality: Triethylamine (TEA; 3 equiv) and MsCl (Ms = mesylate; 2 equiv) were added to a stirred solution of primary carbohybrid **3–5** (1 equiv) in anhydrous CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 2 h, diluted with CH_2Cl_2 and washed with brine. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was dried over anhydrous Na_2SO_4. After removal of the organic solvent under reduced pressure, the crude mesylated product was dissolved in methanol, followed by the addition of *p*-TsOH (1.5 equiv). After stirring for 8 h at room temperature, the solvent was removed under the reduced pressure, and the residue was partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layer was dried over anhydrous Na_2SO_4. The filtrate was condensed under reduced pressure and subjected to flash column chromatography. The detritylated product (1 equiv) was dissolved in DMF and NaN_3 (5 equiv) was added, after which the mixture was stirred at 100 °C for 12 h. The solvent was removed and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was dried over anhydrous Na_2SO_4. The filtrate was condensed under reduced pressure and subjected to flash column chromatography to obtain key intermediates **6–8**. Intermediate **6a**: Prepared from carbohybrid **3a**, white syrup. Yield: 62%; $[\alpha]_D^{25}=-55.11$ ($c=0.74$, $CHCl_3$); $R_f=0.19$ (EtOAc/hexane 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.31$ (s, 2H), 7.22–7.18 (m, 4H), 6.86–6.84 (m, 4H), 4.63 (s, 2H), 4.47–4.43 (m, 2H), 4.23 (d, $J=11.2$ Hz, 1H), 3.80 (s, 6H), 3.65 (t, $J=5.4$ Hz, 1H), 3.60 (d, $J=4.9$ Hz, 2H), 3.26 (q, $J=5.1$ Hz, 1H), 3.22 (s, 6H), 1.94 ppm (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=162.4$, 159.51, 159.49, 157.6, 130.3, 129.9, 129.8, 129.6, 117.9, 114.0, 113.9, 81.1, 78.4, 74.9, 70.6, 63.5, 62.3, 55.39, 55.36, 37.3 ppm; HRMS (FAB+): m/z calcd for $C_{26}H_{32}N_6O_5$ $[M+H]^+$: 509.2512; found: 509.2515.

General procedure for the preparation of morpholine-fused triazoles 9: NaH (2 equiv) was added to a stirred solution of key intermediates **6–8** in anhydrous DMF at 0 °C. After stirring the mixture for 15 min at 0 °C, alkynyl halide (1.5 equiv) was added, and the mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and brine. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was dried over anhydrous Na_2SO_4. The filtrate was condensed under reduced pressure and dissolved in toluene. The mixture was heated to reflux for 4 h. After removal of the solvent, the residue was subjected to flash column chromatography. In some cases, the crude mixture in DMF was heated to 110 °C to give morpholine-fused triazoles **9** in a one-pot manner. After completion of the reaction, the purification step was the same as described above. Triazole **9b**: prepared from intermediate **6a** and 1-bromo-2-butyne; white solid. Yield: 89%; $[\alpha]_D^{25}=-60.08$ ($c=0.58$, $CHCl_3$); $R_f=0.09$ (EtOAc/hexane 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.25$ (s, 2H), 7.15–7.10 (m, 4H), 6.80–6.78 (m, 4H), 4.62–4.50 (m, 4H), 4.45–4.40 (m, 2H), 4.34 (d, $J=11.2$ Hz, 1H), 4.15–4.10 (m, 3H), 3.76–3.74

(m, 7H), 3.18 (s, 6H), 2.08 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=162.1, 159.4, 159.3, 157.7, 136.6, 130.2, 129.84, 129.79, 129.7, 127.5, 117.7, 113.8, 80.4, 77.4, 74.8, 70.0, 64.7, 62.0, 56.0, 55.33, 55.31, 37.2, 9.8 ppm; HRMS (FAB+): *m/z* calcd for $C_{30}H_{36}N_6O_5$ $[M+H]^+$: 561.2825; found: 561.2821.

General procedure for the preparation of 2-morpholione-fused triazoles 10: Diisopropyl azodicarboxylate (1.2 equiv) was added slowly to a stirred solution of key intermediates **6–8** (1 equiv), triphenylphosphane (1.2 equiv), and akynic acids (1.2 equiv) in anhydrous THF at 0°C. The mixture was stirred at 0°C for 1.5 h. After removal of the solvent, the residue was subjected to flash column chromatography to give ester intermediates. They were dissolved in DMF and heated in a capped microwave vessel under microwave irradiation (150 W, 120°C) for 3 min. After removal of the solvent, the residue was subjected to flash column chromatography. Triazole **10a**: Prepared from intermediate **6a** and 2-butynoic acid, yellow solid. Yield: 95%; $[\alpha]_D^{25}=-16.09$ (c=0.61, $CHCl_3$); R_f=0.19 (EtOAc/hexane 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.42 (s, 2H), 7.14 (d, J=8.7 Hz, 2H), 7.03 (d, J=8.7 Hz, 2H), 6.85–6.76 (m, 4H), 4.68–4.64 (m, 1H), 4.54 (d, J=5.8 Hz, 1H), 4.46–4.40 (m, 3H), 4.33 (d, J=10.5 Hz, 1H), 4.23 (d, J=10.5 Hz, 1H), 4.16 (d, J=11.1 Hz, 1H), 3.92–3.89 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.22 (s, 6H), 2.54 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=162.6, 159.8, 159.7, 158.1, 156.7, 148.9, 131.0, 130.1, 129.2, 128.4, 121.8, 117.0, 114.1, 114.0, 79.3, 77.4, 74.9, 70.6, 68.5, 55.7, 55.5, 55.4, 37.3, 11.4 ppm; HRMS (FAB+): *m/z* calcd for $C_{30}H_{34}N_6O_6$ $[M+H]^+$: 575.2618; found: 575.2622.

General procedure for the preparation of piperazine-fused triazoles 11: Diisopropyl azodicarboxylate (1.5 equiv) was added slowly to a stirred solution of key intermediates **6–8** (1 equiv), triphenylphosphane (1.5 equiv), and akynic sulfonamides (1.5 equiv) in anhydrous THF at 0°C. The mixture was stirred at room temperature for 12 h. After removal of the solvent, the residue was subjected to flash column chromatography, and the resulting intermediate was stirred in toluene heated at reflux for 3 h. After removal of the solvent, the residue was subjected to flash column chromatography. Triazole **11b**: prepared from intermediate **6a** and 4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide, yellow solid. Yield: 73%; $[\alpha]_D^{25}=-50.39$ (c=0.46, $CHCl_3$); R_f=0.20 (EtOAc/hexane 2:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.39 (s, 2H), 7.60–7.55 (m, 4H), 7.46–7.43 (m, 2H), 7.37–7.32 (m, 3H), 7.08–7.03 (m, 4H), 6.77–6.71 (m, 4H), 4.72–4.67 (m, 2H), 4.46 (d, J=11.7 Hz, 1H), 4.34–4.19 (m, 3H), 4.15–4.09 (m, 2H), 4.02 (d, J=11.7 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.52 (dd, J=13.1, 5.7 Hz, 1H), 3.17–3.13 (m, 7H), 2.46 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.4, 159.59, 159.57, 157.9, 144.9, 141.9, 132.8, 130.8, 130.6, 130.4, 129.5, 129.1, 129.0, 128.2. 127.8, 126.3, 125.4, 117.5, 113.99, 113.98, 80.2, 75.1, 74.8, 69.8, 57.2, 55.4, 55.3, 44.4, 42.8, 37.3, 21.8 ppm; HRMS (FAB+): *m/z* calcd for $C_{42}H_{45}N_7O_6S$ $[M+H]^+$: 776.3230; found: 776.3234.

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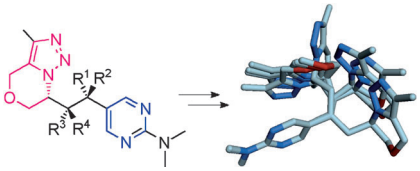
Fused-Ring Systems

*D. Lim, S. B. Park** ..... ▮▮▮▮–▮▮▮▮

Synthesis of Molecular Frameworks Containing Two Distinct Heterocycles Connected in a Single Molecule with Enhanced Three-Dimensional Shape Diversity



A privileged few: Molecular frameworks were synthesized from carbohydrates through the incorporation of two unique privileged substructures connected by stereodivergent diol linkers (see scheme). The vicinal diols were modified by tethering chemistry to maximize molecular-shape diversity through the distinct display of two privileged substructures in 3D space, namely, the linker diversification strategy.