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Privileged Substructure-Based Diversity-Oriented Synthesis Pathway for Diverse Pyrimidine-Embedded Polyheterocycles

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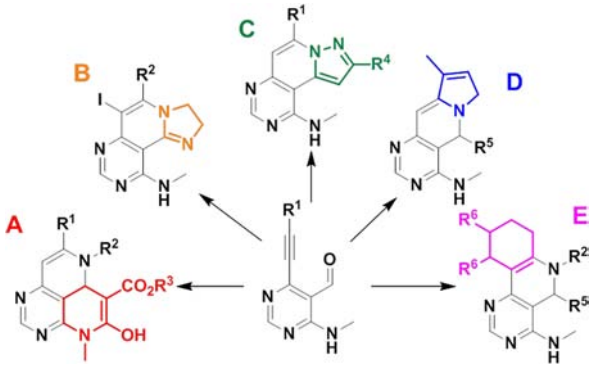
ABSTRACT



A new diversity-oriented synthesis pathway for the fabrication of a pyrimidine-embedded polyheterocycles library was developed for potential interactions with diverse biopolymers. Five different pyrimidine-embedded core skeletons were synthesized from *ortho*-alkynylpyrimidine carbaldehydes by a silver- or iodine-mediated tandem cyclization strategy. The resulting polyheterocycles possess diverse fused ring sizes and positions with potential functionalities for further modification.

Facile fabrication of a structurally diverse small-molecule library plays a crucial role in drug discovery and chemical biology.[1] In particular, the unbiased collection of drug-like small molecules has become an inevitable resource[2] because it can provide a unique opportunity for the identification of novel chemical entities from phenotype-based screening, which is the leading approach for the development of first-in-class drugs.[3] Therefore, an efficient strategy for the expansion of molecular diversity is in great demand in the scientific community. Among the various approaches, diversity-oriented synthesis (DOS)[4] plays an indispensable role to access the unexplored molecular frameworks with maximum structural and stereochemical diversity.[5] Along with this endeavor, we proposed a privileged substructure-based DOS (pDOS) approach for the efficient generation of distinct polyheterocyclic core skeletons embedded with privileged substructures.[6] We believe that the reconstruction of polyheterocycles decorated around privileged substructures harnesses the high biological relevance of the newly constructed molecular frameworks, which has been demonstrated by the discovery of novel bioactive compounds in diverse therapeutic fields such as cancer,[7] osteoporosis,[8] inflammation,[9] and type II diabetes[10] from a benzopyran-embedded pDOS library. As a continuation of our work

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on the development of novel pDOS pathways, we choose pyrimidine as the key privileged substructure. Pyrimidine has been extensively explored in synthetic and medicinal chemistry owing to its unique mimicking of nucleosides and hydrogen bonding ability with nucleic acids in biological systems. In fact, the pyrimidine ring system is common in various bioactive small molecules such as antibacterial agents,[11] cannabinoid receptor 2 agonists,[12] adenosine A3 receptor antagonists,[13] and dipeptidyl peptidase-4 inhibitors[14] (Figure 1).

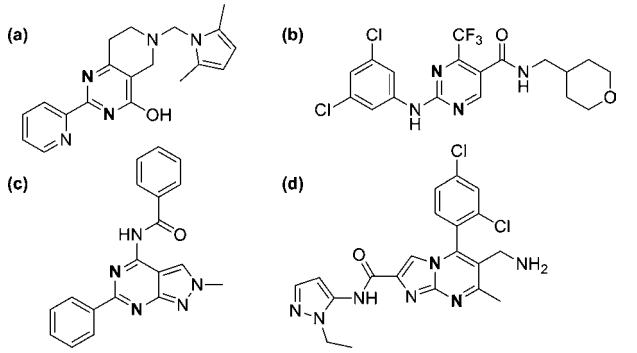

Figure 1. (a) Bacterial protein synthesis inhibitor. (b) Cannabinoid receptor 2 selective agonist. (c) Adenosine A_3 receptor antagonist. (d) Dipeptidiyl peptidase-4 (DPP4) inhibitor.

Pyrimidine-containing polyheterocycles might function as small-molecule modulators that perturb unexplored biological systems, particularly protein−protein interaction. Although a vast number of pyrimidine-containing bioactive compounds are known, their structural frameworks are mainly limited to monocyclic or bicyclic skeletons, probably because of the usual design strategy of pyrimidine as nucleoside analogs. Herein, we describe a new pDOS strategy for the systematic fabrication of polyheterocyclic molecular frameworks around a pyrimidine ring to expand the molecular diversity beyond monocyclic and bicyclic pyrimidine skeletons.

For the efficient fabrication of pyrimidine-containing polyheterocycles, we first designed and synthesized a key substrate, *ortho*-alkynylpyrimidine carbaldehyde **1**,[15] which can be easily converted to imines or hydrazones, followed by a coinage-metal-catalyzed or halogen-promoted 6-*endo*

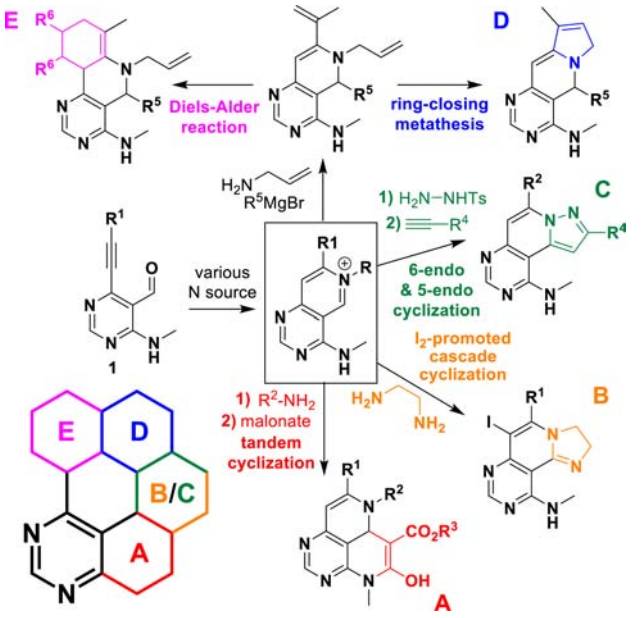

Figure 2. Diversity-oriented synthesis pathways for preparation of pyrimidine-embedded polyheterocycles.

cyclization process to afford bicyclic iminiums[16−19] as the key intermediate. This key intermediate can be transformed into five different pyrimidine-containing polyheterocycles (A−E) under different reaction conditions (Figure 2). Malonates (scaffold A), diaminoalkanes (scaffold B), and terminal alkynes (scaffold C) were separately reacted with each iminium intermediate, which allows the subsequent tandem cyclization via amide formation, iodine-promoted cyclization,[18] and Ag-mediated 5-*endo* cyclization,[19] respectively. In order to obtain different orientations and ring topology of the pyrimidine-containing polyheterocycles (scaffolds D and E) obtained from the above-mentioned scaffolds, we introduced R^1 and R^2 substituents as the biasing elements in the bicyclic intermediates prepared via Ag-catalyzed 6-*endo* cyclization followed by the nucleophilic addition of Grignard reagents. The resulting bicyclic intermediates can be transformed to scaffolds D and E via ring-closing metathesis using Grubbs' second-generation catalyst and a Diels−Alder reaction with dienophiles, respectively.

For the preparation of scaffold A, key substrates **1a** and **1b** were reacted with various amines to afford the *ortho*-alkynylpyrimidyl aldimines, followed by Ag-mediated 6-*endo* cyclization of the imines with the internal alkyne to generate the pyridinium intermediates.[16] Next, the nucleophilic addition of dialkylmalonates with the pyridinium intermediate and subsequent lactamization of the

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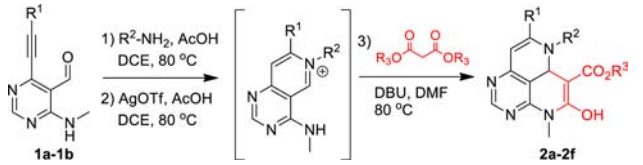
Table 1. Exploration of Scaffold A[a]

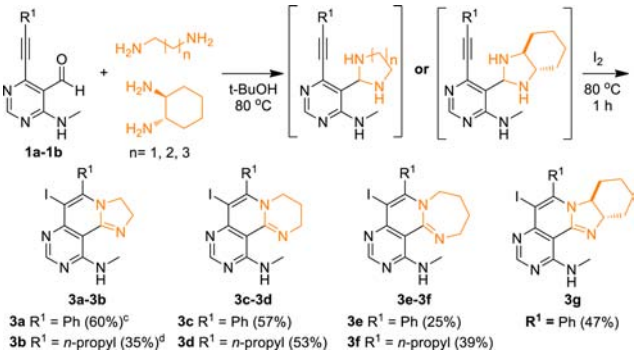


product	R^1	R^2	R^3	yield (%)[b]
2a	phenyl	4-MeO-Ph	ethyl	74
2b	phenyl	4-MeO-Ph	methyl	70
2c	phenyl	2-methoxyethyl	methyl	97
2d	*n*-propyl	4-MeO-Ph	ethyl	84
2e	*n*-propyl	4-MeO-Ph	methyl	83
2f	*n*-propyl	2-methoxyethyl	methyl	77

[a] See the Supporting Information for detailed experimental procedures. [b] Isolated two-step yields from imines (**1d**–**1g**).

esters with the methylamine moiety at the C-4 position of the pyrimidine afforded the pyrimidine-containing tricyclic cores (Table 1). The resulting tricyclic cores spontaneously underwent keto–enol tautomerism to afford **2a**–**2f** because of the conjugation effect from ester group and the additional stabilization by intramolecular hydrogen bonding. The resulting hydroxyl group may be more useful than an amide group for rapid expansion of molecular diversity. This tandem cyclization procedure afforded six tricyclic compounds **2a**–**2f** with different substituents in good to excellent yields (Table 1).

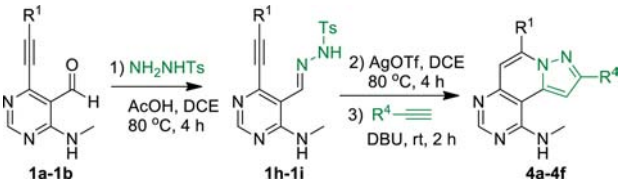
Scheme 1. Exploration of Scaffold B[a,b]



[a] See the Supporting Information for detailed experimental procedures. [b] Isolated yields. [c] Fully aromatized product **3h** was obtained in 10% yield. [d] Fully aromatized product **3i** was obatined in 34% yield.

The reactions of electrophilic *ortho*-alkynylaldehyde **1a** and **1b** with diaminoalkanes afforded the cyclic aminal intermediates,[17] which were transformed into scaffold B via iodine-mediated tandem cyclization (Scheme 1).[18] In this one-pot procedure, iodine not only functioned as the oxidizing agent for the imidazolidine ring formation but also activated the internal alkyne for the 6-*endo* cyclization process. Pyrimidine-containing polyheterocycles (**3a**–**3g**, scaffold B) with different ring sizes and additional fused rings were simply prepared by changing the length or the substituents of the diaminoalkanes (Scheme 1). To further expand the molecular diversity, the vinyl iodide group in scaffold B can be functionalized via palladium-mediated cross-coupling reactions, which has not been explored in this study.

Table 2. Exploration of Scaffold C[a]



product	R^1	R^4	yield (%)[b]
4a	phenyl	phenyl	64
4b	phenyl	cyclopropyl	72
4c	phenyl	1-methylethenyl	51
4d	*n*-propyl	phenyl	70
4e	*n*-propyl	cyclopropyl	69
4f	*n*-propyl	1-methylethenyl	69

[a] See the Supporting Information for detailed experimental procedures. [b] Isolated two-step yields from hydrazones.

For the preparation of scaffold C, a tosylhydrazine group was introduced to *ortho*-alkynylaldehyde in **1a** and **1b**, and the resulting hydrazone intermediates **1h**–**1i** were converted to pyrazolopyrido[4,3-*d*]pyrimidines via Ag-catalyzed 6-*endo* tandem cyclization with the internal alkyne to afford isoquinolinium intermediates, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed nucleophilic addition of R_4-containing terminal alkynes. Subsequent intramolecular 5-*endo* cyclization and aromatization[19] afforded scaffold C (Table 2). The substrate scope of this cascade cyclization was demonstrated to be very diverse because it could accommodate alkyl, aryl, and vinyl acetylenes at the R^4 position to afford pyrimidine-containing tricycles **4a**–**4f** in moderate to good yields (Table 2).

For the synthesis of scaffolds D and E, a vinyl group at the R^1 position of key substrate **1c** was necessary; therefore, the key intermediates **1l**–**1q** were prepared by the reaction of **1c** with allylic or homoallylic amines to afford *ortho*-alkynyl aldimines (**1j**–**1k**), which were diversified by nucleophilic addition with three different Grignard reagents. Using ring-closing metathesis (RCM) with Grubbs' second-generation catalyst, intermediates **1l**–**1q** were converted to scaffold D, **5a**–**5c** and **6a**–**6c**, fused with 5- and 6-membered rings, respectively. Diels–Alder reaction of the diene moiety in intermediates **1l**–**1n** with substituted maleimides afforded scaffold E with pyrimidine-containing tetracycles **7a**–**7f** (Table 3).

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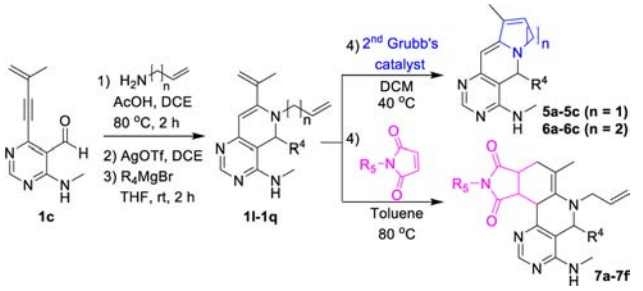
Table 3. Exploration of Scaffold D and E[a]



product	SM[b]	n	R^4	R^5	yield (%)[c]
5a	**1l**	1	methyl	–	50
5b	**1m**	1	phenyl	–	48
5c	**1n**	1	4-MeO-Ph	–	48
6a	**1o**	2	methyl	–	48
6b	**1p**	2	phenyl	–	60
6c	**1q**	2	4-MeO-Ph	–	52
7a	**1l**	1	methyl	phenyl	36
7b	**1m**	1	phenyl	phenyl	32
7c	**1n**	1	4-MeO-Ph	phenyl	42
7d	**1l**	1	methyl	4-MeO-Ph	34
7e	**1m**	1	phenyl	4-MeO-Ph	36
7f	**1n**	1	4-MeO-Ph	4-MeO-Ph	32

[a] See the Supporting Information for detailed experimental procedures. [b] SM stands for starting materials for olefin metathesis and Diels–Alder reaction. SM was prepared from imines (**1j**–**1k**) from **1c** via the first synthetic step. [c] Isolated yields from **1l**–**1q**.

As stated earlier, we aimed to construct molecular diversity using the pDOS strategy, particularly with diverse polyheterocycles around a pyrimidine substructure, which is schematically illustrated in Figure 3a. After fabricating five unique core skeletons, we clearly demonstrated the diverse orientation of each polyheterocycle with wide spatial coverage by *in silico* generation of the energy-minimized conformers and overlaying them in a three-dimensional (3D) space with the alignment of pyrimidine substructure (Figure 3b). We also performed the principal moment of inertia (PMI) analysis[20] to capture the shape-based distribution of small molecules as dots in an isosceles triangle defined by vertices (0,1), (0.5,0.5), and (1,1), which correspond to the rod, disc, and sphere shapes, respectively. As shown in Figure 3c, five representative scaffolds and two key intermediates were dispersed in the PMI plot, indicating excellent diversity in the shape of each scaffold. Along with shape differences, we clearly visualized that the resulting five color-coded scaffolds were widely distributed in a 3D chemical space with maximum molecular diversity calculated by using unbiased molecular descriptors and analyzed by principal component analysis (PCA, Figure 3d). The molecular diversity of five different scaffolds was differentiated mainly by the topological polar surface area, van der Waals (VDW) surface area, and VDW volume.

In summary, we have developed a new pDOS strategy with pyrimidine as the privileged substructure. The

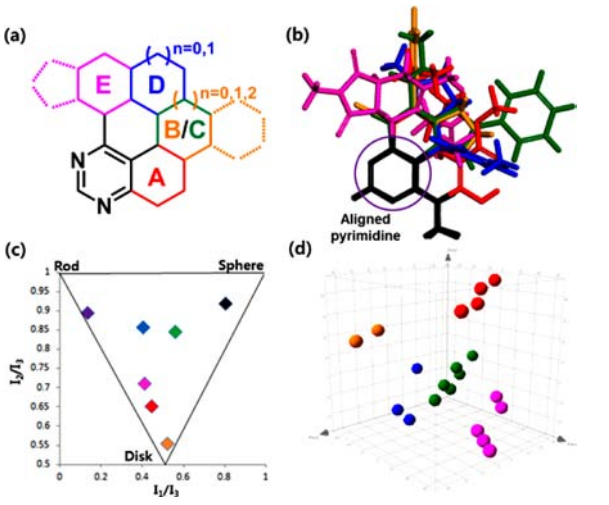


Figure 3. (a) Schematic figure for spatial coverage around the pyrimidine substructure with five unique core skeletons in different colors; (b) overlay of energy-minimized conformers of five core skeletons with the alignment of the pyrimidine substructure in their own color codes; (c) PMI plot depicting five core skeletons in their own color codes along with intermediate **1a** and **1l** in violet and black colors, respectively; (d) PCA of five different pyrimidine-containing polyheterocycles. Compounds from each skeleton were differently color-coded.

resulting five scaffolds consist of unique pyrimidine-embedded polyheterocycles fused with different ring sizes and orientations. Scaffolds A–C were synthesized by silver- or iodine-mediated 6-*endo* cyclization followed by tandem cyclization with different reactants. Scaffolds D and E were prepared from bicyclic intermediates **1l**–**1q** followed by a RCM or Diels–Alder reaction. The molecular diversity of each scaffold was successfully confirmed by a series of computational studies, structural alignment of energy-minimized 3D conformers, shape diversity studies using PMI analysis, and *in silico* PCA analysis. This pDOS strategy allows the fabrication of unique polyheterocycles along with wide spatial coverage around pyrimidine as the privileged substructure that ensures high potential for molecular interactions with biopolymers in a selective and specific manner.

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Supporting Information Available. Experimental details, copies of ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.