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Rapid Generation of Privileged Substructure-Based Compound Libraries with Structural Diversity and Drug-Likeness

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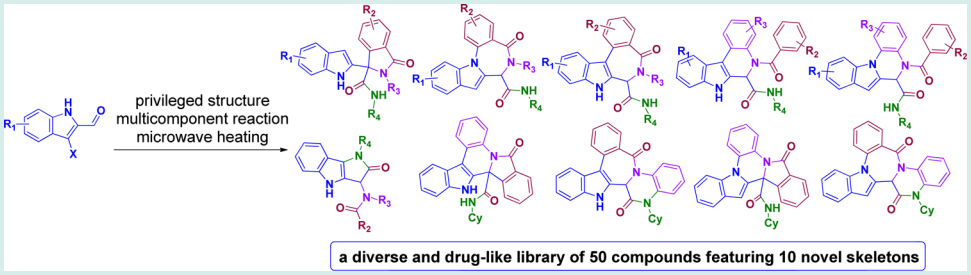
Supporting Information



ABSTRACT: A library of privileged-substructure-based, heterocyclic compounds was constructed by a sequence of Ugi four-component reactions incorporating the indole motif and microwave-assisted cyclizations in branched pathways. Cheminformatic analysis confirmed that the library exhibited a high degree of structural diversity and good drug-likeness.

KEYWORDS: *indole, diversity-oriented synthesis, drug-like, privileged structure, microwave*

INTRODUCTION

An increasing number of therapeutic targets have been identified due to the rapid advances in genomics and proteomics. This has created a tremendous need to develop more efficient methods to generate new chemical libraries used for drug screening.[1] It is recognized that molecular skeletons are more important than the appendices for high-throughput screening, and a compound library featuring a high degree of skeletal diversity can effectively increase the occupation of "chemical space", thus improving the hit rates for diverse biological targets in "biological space".[2] However, the hit rates of most of current combinatorial libraries are far from satisfactory. This is often attributed to the lack of structural diversity in these libraries which traditionally yield similar molecular skeletons decorated with different substituents. In addition to diversity, high-quality compound libraries are expected to display good drug-like properties.[3] A diverse library created with little consideration of drug-like properties may be subjected to more absorption, distribution, metabolism, excretion, and toxicity (ADME/T) problems during the drug discovery process. The concept of diversity-oriented synthesis[4] around privileged structures, defined as rational DOS or privileged-substructure-based DOS (pDOS), has been proven as a powerful tool to construct high-quality compound libraries.[5] Even though, the development of robust strategies to create diverse molecular architectures embedded with privileged structures remains a demanding challenge and is highly desirable for improving the success of biological screenings.[6] We herein introduce an efficient strategy which allows rapid access to pDOS libraries encompassing molecular complexity, structural diversity, and drug-like properties.

RESULTS AND DISCUSSION

Library Construction. Multicomponent reactions (MCRs) provide an efficient complexity-generating approach to easily transform three or more starting materials into a single product in an atom- and step-economical way.[7] Privileged structures offer an ideal source of lead compounds for drug discovery due to their inherent affinity for diverse biological targets.[8] Microwave heating can speed up a broad range of organic reactions compared to conventional heating conditions.[9] Combining these ideas, we proposed a sequential procedure of a versatile MCR incorporating a privileged structural motif in the modular inputs, and subsequent branched post-MCR transformations under microwave heating. This may serve as a flexible and robust strategy to rapidly access diverse and drug-like libraries.

As a demonstration, we selected the Ugi reaction[10] as the MCR, indole as the privileged structure, and microwave-assisted intramolecular cyclizations as the post-transformations (Scheme 1). Indole motifs represent one of the most prominent privileged structures and are ubiquitous in natural products and pharmaceutical compounds.[11] More importantly, from the point of view of diversity, there are at least three reactive sites in the indole structure, with the potential for

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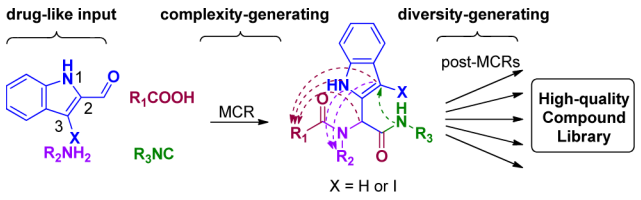
Scheme 1. Strategy to Create a Diverse and Drug-Like Library of Polycyclic Scaffolds



divergent synthesis. For example, selective N1, C2, or C3-arylation of indoles has received numerous developments in recent years.[12] Considering the diverse biological and chemical properties of indole, we chose to incorporate this versatile motif in the aldehyde component of the Ugi reactions. In the first step, high levels of molecular functionality are incorporated to provide various linear Ugi adducts. The iodide functionality acts as a leaving group in the subsequent nucleophilic cyclizations and can be alternately incorporated into each component of the Ugi reactions to increase the structural diversity of the final library. These Ugi products then served as precursors which participated in the subsequent selective post-transformations under different conditions in a branched manner. In addition, the diversity level can be further enhanced by third-step transformations if the Ugi substrates are equipped with additional distinct reactive sites such as two pairs of iodide functionalities. When these post-Ugi transformations are conducted under microwave heating, the creation of pDOS library can be greatly accelerated.

In our previous work, we have successfully prepared three distinct sets of indole-based heterocycles from the same set of Ugi adducts under microwave heating in a reaction-condition-controlled manner (Scheme 2).[13] The Ugi products **5** were synthesized by condensation of 1*H*-indole-2-carbaldehydes **1**, 2-iodobenzoic acids **2**, amines **3**, and isocyanides **4**. The linear precursors **5** contain five potential nucleophilic sites, i.e. indole C3, indole N1, the α-C of the secondary amide, the oxygen and NH of the secondary amide. The iodide functionality in the benzoyl moiety of **5** acts as a directing group in the subsequent cyclizations. In light of the distinctive nucleophilicity and affinity of the reactive sites in **5** for different promoters, deliberate choice of reaction conditions allowed regioselective cyclizations to form diverse heterocyclic compounds. Specifically, treatment of **5** with cesium carbonate (Cs_2CO_3) provided exclusively **6** through an unprecedented metal-free intramolecular sp^3-hybridized C−H arylation. When substrates **5** were subjected to copper catalysis, N1-arylation products **7** were preferentially formed; whereas, palladium catalysis led to intramolecular C3-arylation products **8**. These protocols have valuable features of easily available Ugi inputs, broader substrate scope, operational simplicity, step economy, high yields, and short reaction time.

Further, the diversity was expanded by incorporating the directing iodide group to the amine input of the Ugi reaction (Scheme 2).[14] The acyclic, peptide-like α-acylaminoamides **11** were obtained by similar Ugi condensations from 1*H*-indole-2-carbaldehydes **1**, carboxylic acids **9**, 2-iodoanilines **10**, and isocyanides **4**. Simply switching the catalytic systems of **11** provided two skeleton-diversifying branches. Specifically, copper iodide promoted intramolecular N1-arylation reactions leading to **12**, while palladium acetate triggered intramolecular C3-arylations to provide **13**. In all cases, the divergent sequences gave moderate to good yields.

To further expand the scope of this strategy, we herein shifted the directing iodide group to the aldehyde input of the Ugi reaction, to allow the synthesis of 6−5−5 polycyclic heterocycles (Scheme 2). The linear substrates **15** were obtained from the four-component Ugi reaction between 3-iodo-indole-2-carbaldehyde **14**, carboxylic acids **9**, amines **3**, and isocyanides **4**. Selected examples of the assayed conditions based on substrate **15a** are shown in Table 1. Preliminary optimization of the cyclization conditions demonstrated that copper catalysis was not effective for the formation of the indole-fused polycyclic compound **16a**. A considerable amount of deiodination byproduct **17** was isolated (entry 1, Table 1), which may be caused by moisture in the solvent.[15] The palladium-catalyzed cross-coupling of a nitrogen nucleophile with an aryl halide is known as the Buchwald−Hartwig reaction.[16] The proper choice of catalyst, ligand, base, and solvent in Buchwald−Hartwig chemistry is crucial for the success of a given amidation reaction. Initial exploration into the intramolecular Buchwald−Hartwig reaction of **16a** involved an investigation of the palladium catalytic system. Among various catalysts, tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) has been shown to work well in combination with biaryldialkylphosphines[16] in many instances. Using the $Pd(OAc)_2/PPh_3$ system failed to promote the transformation, and Pd-catalyzed fragmentation[17] by oxidative cleavage of α-arylamino amide **15a** to α-ketoamide was detected using TLC and LC/MS analysis (entry 2, Table 1). These results indicated that the cyclization needs to be conducted under anaerobic conditions and in an anhydrous solvent. Bidentate ligand 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) did not lead to any desired product (entry 3, Table 1). Zhu et al. recently reported similar intramolecular Buchwald−Hartwig reactions;[18] however, under Zhu's conditions, dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) and 2-dicyclohexylphosphino-2′-methylbiphenyl (MePhos) also resulted in low yields, even when the temperature was raised to 150 °C (entries 4−7, Table 1). The incomplete conversion of the starting material is likely a consequence of the poor heating ability of low-polarity solvents under microwave irradiation. Indeed, the use of polar solvent as DMF allowed for rapid heating of the reaction mixture, and all the starting material was consumed. The reaction afforded a higher yield of the desired product **16a** in DMF than in acetonitrile or toluene (entries 8−10, Table 1). Eventually, this reaction was best effected using a combination of $Pd_2(dba)_3$, XPhos, and K_2CO_3 at 130 °C in DMF under anaerobic condition (entry 8, Table 1).

This optimized condition was then transferred to the synthesis of several 6−5−5 polycyclic heterocyclic compounds **16**. Under the reaction condition, all derivatives were smoothly converted into the tricyclic derivatives with moderate to good yields (Scheme 2). The arylation was a slightly sensitive to steric hindrance effects, and a decreased product yield was observed when starting from the more hindered butyl isocyanide.

However, this is not the end of our chemistry story. We envisioned that the modular four-component Ugi reaction and the versatile chemistry of Ugi adducts may provide further skeletal diversification when two directing iodide groups were introduced. A sequenced process via initial generation of Ugi product **18** and subsequent divergent intramolecular cyclizations produced various heterocyclic compounds possessing distinct skeletons (Scheme 2). In this synthetic plan, particularly noteworthy are the reactivity differences toward

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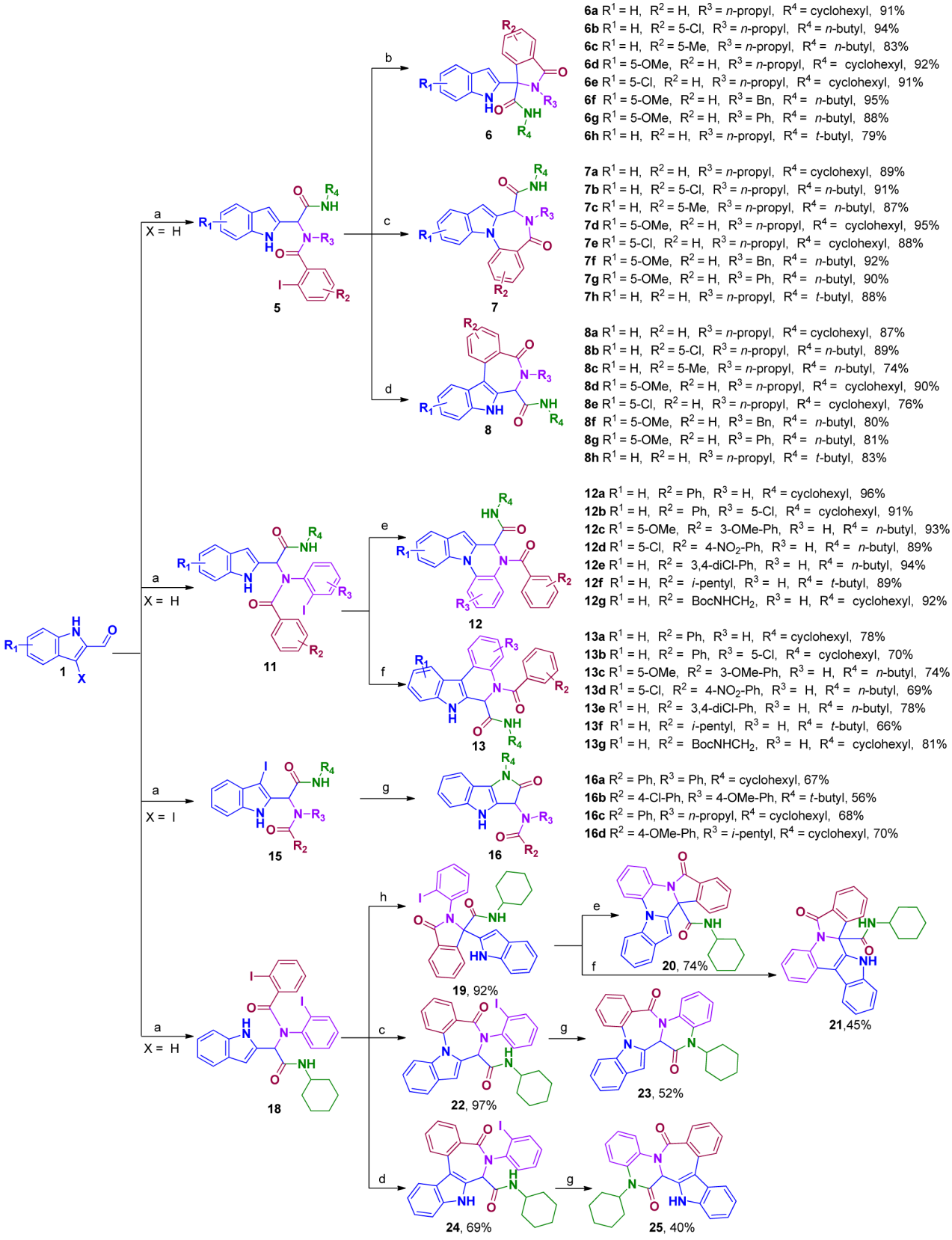
Scheme 2. Construction of Indole-Based Library of Heterocyclic Compounds from Indole-2-Carbaldehyde via Ugi Four-Component Reactions and Subsequent Divergent Cyclizations Under Microwave Heating[a]



[a]Reagents and conditions: (a) acids, amines, isocyanides, MeOH, rt for products **5**, **11**, and **18**, 40 °C for products **15**, 3 d. (b) Cs_2CO_3, DMSO, MW, 80 °C, 40 min. (c) CuI, L-proline, K_2CO_3, DMSO, MW, 80 °C, 40 min. (d) $Pd(OAc)_2$, PPh_3, K_2CO_3, dioxane/MeCN = 3/1 (v/v), MW, 110 °C, 2 h. (e) CuI, L-proline, K_2CO_3, DMSO, MW, 90 °C, 40 min. (f) $Pd(OAc)_2$, PPh_3, K_2CO_3, dioxane/MeCN = 3/1 (v/v), MW, 130 °C, 2 h. (g) $Pd_2(dba)_3$, XPhos, K_2CO_3, DMF, MW, 130 °C, 20 min. (h) Cs_2CO_3, DMSO, MW, 60 °C, 40 min.

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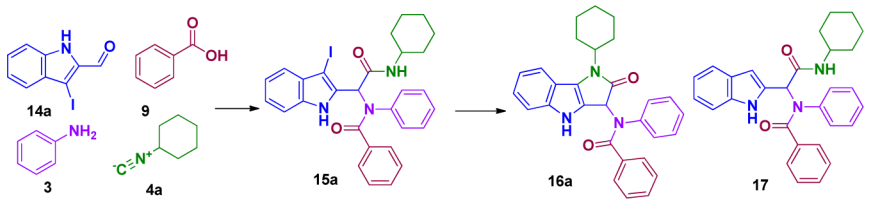
Table 1. Survey of Reaction Conditions for the Post-transformation of 15a



entry	condition[a]	yield of **16a** (%)[b]
1	CuI, L-proline, K_2CO_3, 90 °C, 40 min, DMSO	(92)[c]
2	$Pd(OAc)_2$, PPh_3, K_2CO_3, dioxane/CH_3CN = 1:1, 130 °C, 1 h	<10[d]
3	$Pd_2(dba)_3$, XantPhos, K_2CO_3, PhMe/CH_3CN = 3:1, 150 °C, 1 h	0
4	$Pd_2(dba)_3$, MePhos, K_2CO_3, PhMe/CH_3CN = 3:1, 100 °C, 2 h	<10[d]
5	$Pd_2(dba)_3$, MePhos, K_2CO_3, PhMe/CH_3CN = 3:1, 150 °C, 2 h	40[d]
6	$Pd_2(dba)_3$, XPhos, K_2CO_3, PhMe/CH_3CN = 3:1, 150 °C, 2 h	34[d]
7	$Pd_2(dba)_3$, MePhos, K_2CO_3, dioxane/CH_3CN = 3:1, 150 °C, 2 h	43[d]
8	**$Pd_2(dba)_3$, XPhos, K_2CO_3, DMF, 130 °C, 20 min**	**67**
9	$Pd_2(dba)_3$, XPhos, K_2CO_3, CH_3CN, 130 °C, 20 min	48
10	$Pd_2(dba)_3$, XPhos, K_2CO_3, PhMe, 150 °C, 2 h	30[d]

[a] **15a** (1.0 equiv), metal catalyst (0.05 equiv), ligand (0.1 equiv), and base (2.0 equiv) in solvent under nitrogen protection, MW. [b] Isolated yield. [c] Yield of **17**. [d] **15a** was recovered.

nucleophilic substitution exhibited by the two directing iodide groups installed in molecule **18**. First, the aryl iodide on the aniline ring is less reactive than that on the benzoyl moiety. Selective arylations of the latter through inherently different nucleophilic sites provided **19**, **22**, and **24** under the optimal reaction conditions described previously.[13] Then, the second iodide group offers the possibility for further diversification, leading to the polyheterocyclic products **20**, **21**, **23**, and **25** under different catalytic systems with decent yields.[14] Thus, this simple but powerful sequence of reactions created a highly diverse library of fused heterocyclic compounds nearly in a "one-step one-skeleton" manner.

Cheminformatic Analysis. Using our strategy, a small library of 50 indole-based heterocyclic compounds with 10 distinct scaffolds was generated within only two or three steps. The following cheminformatic analysis was then performed to assess the quality of this pDOS library in terms of diversity and drug-likeness. For comparison, several reference sets were also collected: (1) Zinc Set, a diverse subset of small molecules from the ZINC database;[19] (2) Focus Set, a focused library (conventional combinatorial chemistry) considering the fragment diversity;[20] (3) CMC Set, Comprehensive Medicinal Chemistry (CMC) database (Accelrys Software Inc.), an annually updated database which includes data on compounds used or studied as human medicinal agents from 1900 onward; and (4) FDA Drugs, small molecule drugs approved by the FDA.

The data sets were prepared as follows:

(1) Zinc Set: The chemical structure file in SMILES format, containing a total of 19 734 523 purchasable compounds and representing the largest commercially available chemical space, was retrieved from the ZINC database (http://zinc.docking.org accessed on February 16, 2012). The data set was reduced to a manageable subset of 10 000 using the Diverse Molecules component of Pipeline Pilot (PP) 7.5 (Accelrys Software Inc.), which selects diverse compounds with respect to specified molecular properties. Here, the dissimilarity described by FCFP_4 molecular fingerprint[21] and Tanimoto distance was used.

(2) Focus Set: An in-house combinatorial library designed for the discovery of cyclophilin A (CypA) inhibitors[20] was used as another reference. The compounds in this set contain three building blocks, which constitute a CypA-focused compound library with a population of 255 (5 × 3 × 17). PP was used to generate SMILES representations for all members of this set.

(3) CMC Set: The 9099 chemical structures deposited in the CMC database (2011.1 release) were exported in SDF format, and then transformed to SMILES representations using PP.

(4) FDA Drugs: The chemical structure file of the 1410 small molecule drugs approved by the FDA was downloaded in SMILES format from DrugBank[22] (http://www.drugbank.ca accessed on October 12th, 2011).

Diversity Analysis. The normalized principal moment of inertia (PMI) ratio approach formalized by Sauer and Schwartz was used to capture the shape-based distribution of our pDOS library.[2b] First, a set of up to 255 three-dimensional (3D) conformations were generated for each compound, using the Catalyst CAESAR component of Discovery Studio (DS) 2.5 (Accelrys Software Inc.).[23] These conformers were then subjected to energy minimization using the Minimize Molecule component of PP, and the lowest energy conformer was used for the PMI calculations. Default parameter settings were used for components of DS and PP, unless otherwise specified. The two-dimensional characteristic X and Y coordinates of the PMI plot are the ratios of the smallest or medium eigenvalues for the diagonalized mass tensor to the largest (i.e., $X = I_{small}/I_{large}$, $Y = I_{medium}/I_{large}$) and were calculated using the Principal Moments of Inertia component of PP. The points in the resulting plot occupy an isosceles triangle defined by the vertices (0, 1), (0.5, 0.5), and (1, 1), corresponding to the shapes of a rod, disk, and sphere, respectively.

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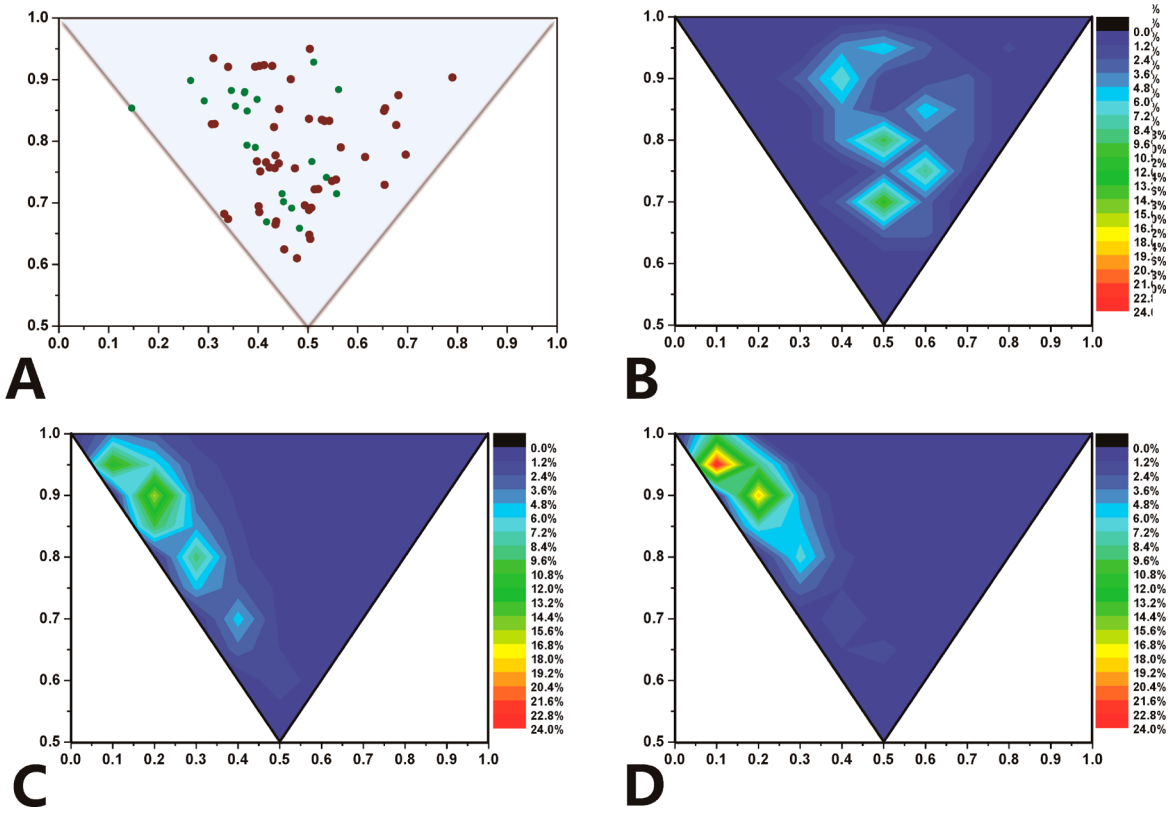

Figure 1. Molecular shape diversity analysis: (A) PMI plot depicting 20 pDOS intermediates (green) and 50 final compounds (red) from this study and heat maps depicting the molecular shape distributions of the data sets, (B) pDOS library, (C) Zinc Set, and (D) Focus Set.

As shown in Figure 1A, the dots representing the 20 intermediates (Ugi products) of the pDOS compounds are colored green, and the 50 final compounds are shown in red. Cleary, the intermediates were dispersedly distributed, and the final compounds further expanded the space covered. This result indicates that our diversity-oriented synthesis proceeded along different pathways upon minor changes in reagents and reaction conditions, allowing access to different chemical space via the production of a wide distribution of compounds. The PMI plot also provides a visual method to compare diversity corresponding to the area of shape space covered by a collection of molecules. Figure 1B–D shows the distribution heat maps for the pDOS library and two reference sets, where regions of a high occurrence rate are represented by warm colors and low occurrence by cold colors. We noted that the pDOS compounds were distributed evenly over the space and populated the central regions among rod-, disk-, and sphere-like shapes; no distinct "hot spots" were observed in the plot. In contrast, the compounds in the Zinc and Focus Sets were mainly located along the left-hand triangle side, adopting a flat and/or elongated molecular shape. The Zinc set compounds spanned nearly the entire range of the left edge of the PMI space, and the Focus set compounds were more densely distributed in the upper-left region. Notably the Focus Set compounds exhibited a hot spot, indicating that combinatorial library design may not be an efficient method to achieve chemical diversity.

The tendency of compound libraries to mainly occupy the left or upper-left sides of the triangle in PMI plots has been reported previously. Wirth and Sauer pointed out that a skewed distribution is characteristic of compound data sets from different origins, even for some biologically relevant collections.[24] Thus, we questioned whether an advantage can be gained to artificially increase the number of spherical compounds in a screening library. However, ligand-binding sites vary widely in size and shape: they can be a curved groove composed of several interconnected subpockets, or a nearly smooth and spherical cavity. For example, catalytic sites of enzyme usually exist as large, deep clefts on the protein surface—many drugs have been observed to bind into the largest surface cavities, which tend to be less spherical overall.[25] In contrast, the ligand-binding domain of pregnane X receptor (PXR) is a typical spherical example,[26] which shows limited orientation specificity and may cause difficulty for designing selective ligand. Clearly, the existence of such spatially distinct sites encourages us to strive for maximum shape diversity in the pDOS-derived compound collection.

Drug-Likeness Analysis. In addition to diversity, high-quality libraries are also expected to exhibit drug-likeness[3] to produce compounds with desirable pharmacokinetic and safety profiles. Much effort has been invested to identify the key differences between drugs and other organic compounds, among which the most widely applied approach is Lipinski's rule of five (RO5) with respect to determining oral drug-likeness.[27] Recently, we reported a distribution analysis of 50 structural and physicochemical properties on different chemical databases.[28] Six molecular saturation and heteroatom proportion-related properties, together with their optimum value ranges, were found to be useful for differentiating between drug-like and non-drug-like databases. These properties are easy to understand and calculate, while can only be used to set the limits that form the drug region. In this study, we defined the *dl* score, an averaged satisfaction ratio of the six molecular

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saturation and heteroatom proportion-related properties, as an index to quantify the drug-likeness of compound collections.

Table 2 summarizes the *dl* scores of our pDOS library and several reference sets. The FDA Drugs yielded the highest score of 0.608, closely followed by the other drug-related set, the CMC Set, with a score of 0.593. For comparison, the collection of common organic chemicals in the Zinc Set produced a much lower *dl* score of 0.370, and the Focus Set combinatorial chemical library had the lowest score of 0.339. As the Zinc Set and Focus Set were included as non-drug-like reference sets in this study, these results clearly demonstrate that the *dl* score is an efficient index for quantitatively differentiating drug-like and nondrug-like databases. Satisfactorily, our pDOS library yielded a high *dl* score of 0.545, which is close to the scores of the drug-related sets and much higher than the other organic screening libraries. Therefore, we may infer from this analysis that pDOS-derived compounds have a significant degree of drug-likeness and may represent a valuable resource for the discovery of novel small-molecule modulators in chemical biology and drug discovery.

Table 2. Drug-Likeness Analysis for the pDOS Library and Several Drug/Non-drug-Related Data Sets

data set	size	*dl* score
Zinc Set	10000	0.370
Focus Set	255	0.339
pDOS Library	70	0.545
CMC Set	9099	0.593
FDA Drugs	1410	0.608

CONCLUSIONS

In summary, we have rapidly constructed a library of 50 privileged-substructure-based heterocyclic compounds within only two or three steps, by integrating the modularity of the Ugi four-component reaction, versatile properties of 1*H*-indole-2-carbaldehyde, regioselective control of divergent post-Ugi transformations, and the enabling technique of microwave heating. This synthetic strategy has various advantageous features, such as readily available inputs, broad substrate scope, operational simplicity, step economy, good yields, and short reaction time. Furthermore, cheminformatic analysis confirmed that the library exhibited a high degree of molecular diversity and good drug-likeness. We anticipate that these novel heterocyclic compounds fused with the bioactive indole motif may find their pharmaceutical applications after further investigations.

EXPERIMENTAL PROCEDURES

General Procedure for Preparation of Ugi Adducts 15 (15a As an Example). To a solution of aniline (1.0 mmol) in dry MeOH (5.0 mL) was added 3-iodo-1*H*-indole-2-carbaldehyde (1.0 mmol), benzoic acid (1.0 mmol), and cyclohexyl isocyanide (1.0 mmol), and the reaction mixture was stirred at 40 °C for 24 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography to give the corresponding Ugi product **15a**.

General Procedure for Preparation of Ugi Adduct 18. To a solution of 2-iodoaniline (1.0 mmol) in dry MeOH (5.0 mL) was added indole-2-carbaldehyde (1.0 mmol), and the reaction mixture was stirred at room temperature for 10 min. After addition of 2-iodobenzoic acid (1.0 mmol), the reaction mixture was stirred for 5 min followed by addition of cyclohexyl isocyanide (1.0 mmol), and the reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure. The residue was purified by flash chromatography to give the corresponding Ugi product **18**.

General Procedure for Preparation of Compounds 16. A high-pressure microwave vessel was loaded with Ugi product **15** (0.04 mmol, 1.0 equiv), $Pd_2(dba)_3$ (0.002 mmol, 0.05 equiv), XPhos (0.004 mmol, 0.1 equiv), and K_2CO_3 (0.08 mmol, 2.0 equiv) in dry DMF (0.02 M). The vessel was degassed, refilled with argon, and sealed. The mixture was subjected to microwave heating at the temperature and power indicated for 20 min. After cooling, the reaction mixture was washed with water and then extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give the corresponding products.

Preparation of 3-Iodoindole-2-Carboxaldehyde 14. An ice-cooled solution of I_2 (1.67 g, 6.6 mmol) in DMF (30 mL) was added to a solution of 2-formylindole (0.96 g, 6.6 mmol) and powdered KOH (1.3 g, 23.8 mmol). After stirring at rt for 4 h, the mixture was poured into a solution of 28% NH_4OH (100 mL) and $NaHSO_3$ (1 g, 9.6 mmol) in water (1.5 L). The precipitates were separated by filtration to give the 3-iodoindole **14** (1.45 g, 81%).

ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR data and spectra for products **6**–**8**, **12**, **13**, **16**, **17**, and **19**–**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

†Lei Zhang and Mingyue Zheng contributed equally to this work.

Notes

The authors declare no competing financial interest.

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