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Solid-Phase Parallel Synthesis of a Tetrahydroindazolone Library Containing Three Unique Core Skeletons

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Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday

Abstract: We have developed a practical strategy for the regioselective synthesis of a 1-(hetero)aryl-3-substituted tetrahydroindazolone library. The condensation of in situ generated arylhydrazine on solid supports with 2-acylcyclohexane-1,3-diones ensured the efficiency of solid-phase parallel synthesis. In addition, we introduced three unique core skeletons containing nitrophenyl, anilyl, and pyridyl groups to maximize the molecular diversity through a diverse display of polar surface area in 3D chemical space. A 162-membered drug-like tetrahydroindazolone library was constructed in an average purity of 92% without further purification.

Keywords: molecular diversity · polar surface area · regioselectivity · solid-phase synthesis · tetrahydroindazolones

Introduction

The importance of molecular diversity has been clearly recognized to identify specific bioactive small molecules for the understanding of mysterious biological processes, which is the core of a new interdisciplinary research area, chemical biology.[1] Since the completion of the Human Genome Project in 2003, biomedical research communities have been focusing on the elucidation of gene functions and the associated control of gene products through the perturbation upon treatment with small-molecule modulators.[2] The discovery of specific small-molecule modulators can lead to the development of potential therapeutic agents.[3] In addition, they can serve as a biomedical research tool to elucidate a wealth of information about complex functions of biopolymers.[4] For the efficient and systematic identification of bioactive small molecules, there is a great demand for the construction of a drug-like compound library with molecular diversity, such as skeletal, stereochemical, and building-group diversity.[5]

To address this unmet need, the organic chemistry community has developed a new algorhythm for the construction of small-molecule libraries containing natural product-like or drug-like skeletons through combinatorial chemistry and diversity-oriented synthesis (DOS).[5] In fact, the practical application of solid-phase organic synthesis has fundamentally changed the thinking process for efficient production of a large number of small molecules due to its advantages, such as simple purification, easy manipulation, amenability to automation, and enforced reaction completion when using a large excess of reagents. Therefore, the development of a new synthetic procedure using solid-phase parallel synthesis can facilitate the rapid construction of a small molecule library with diverse core skeletons. We have been working on the construction of drug-like polyheterocycle libraries embedded with privileged substructures including benzopyrans,[6] pyrroles,[7] carbohybrids,[8] and acetal-fused pyranopyrones.[9] Our research group has also developed a practical solid-phase parallel strategy for the divergent synthesis of skeletally diversified polyheterocycles, such as diazabicycle,[10] Δ^5-2-oxopiperazine,[11] tetrahydro-β-carboline,[12] and tetrahydro-1,4-benzodiazepine[13] from in situ generated cyclic iminiums as a common intermediate. All these molecular frameworks are derived from the structures of bioactive

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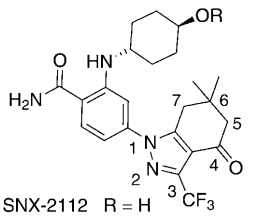
natural products or therapeutic agents and the pilot libraries embedded with these core skeletons were constructed through solid-phase parallel synthesis with high purities and molecular diversity.

As a continuation of our endeavor in molecular diversity using diversity-oriented synthesis, we recognized tetrahydroindazolone as an important pharmacophore. For example, SNX-2112, which contains a tetrahydroindazolone moiety, is reported as a selective antitumor agent with oral bioavailability through the competitive binding at the adenosine triphosphate (ATP) binding site in the N-terminal domain of heat shock protein 90 (HSP90). HSP90 is one of the most abundant proteins in cells and is known to associate with the non-native structure and maturation of many cellular proteins, that's why it is called a molecular chaperone.[14] In cancerous cells, a number of proteins, including various growth factor receptors and signaling proteins, are overexpressed and the stabilization of these mutant proteins are critically regulated by HSP90.[15] Therefore, the inhibition of HSP90 is one of the validated approaches for the treatment of various kinds of cancers.[16] There are many reports regarding HSP90 inhibitors including geldanamycin,[17] its analogues (17-AAG and 17-DMAG),[18] radicicol,[19] CNF-2024,[20] etc. SNX-2112 is currently in phase III clinical trials,[21] which validates the importance of tetrahydroindazolone as a key pharmacophore in biomedical research. However, the systematic exploration of chemical space around privileged tetrahydroindazolones has not yet been extensively pursued. Furthermore, we were interested in the diversification of tetrahydroindazolone-based core skeletons with the preservation of its validated molecular frameworks. Therefore, we developed a practical procedure for the synthesis of tetrahydroindazolone with excellent regioselectivity and accomplished the construction of a novel tetrahydroindazolone library containing three unique core skeletons by using solid-phase parallel synthesis.



SNX-2112 R = H
SNX-5422 R = glycine ester mesylate

Abstract in Korean:

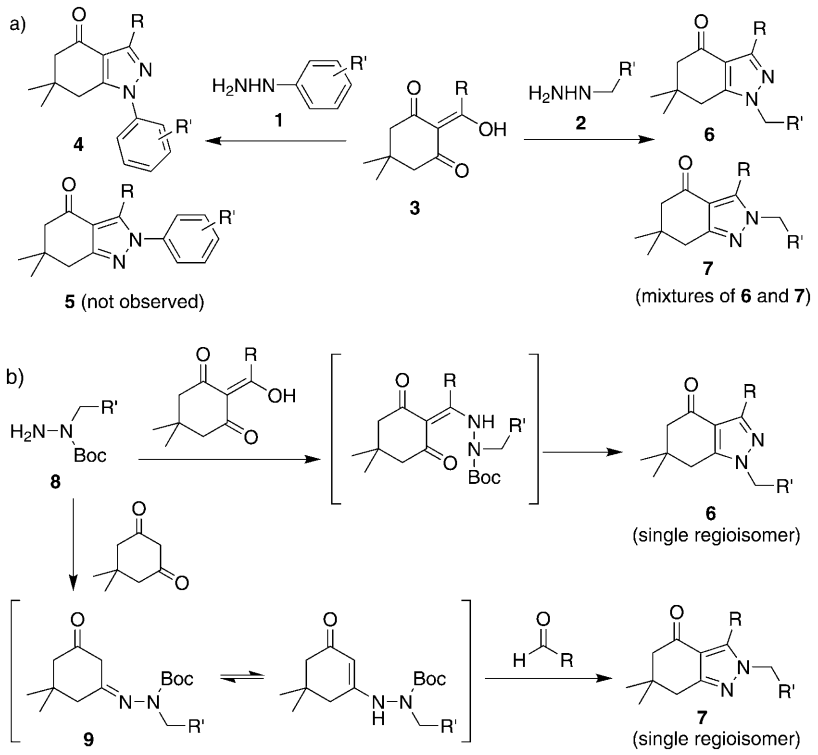
본 연구에서는 효율적인 고체상 병렬합성을 통해서 tetrahydroindazolone 을 중심골격으로 하는 의약유사 저분자 화합물의 합성법을 개발하였다. 최종 생성물의 위치선택성 확보를 위해 고체상에서 만들어진 (hetero)arylhydrazine 과 다양한 치환기를 가진 2-acylcyclohexane-1,3-dione 의 축합반응을 통해서 원하는 tetrahydroindazolone 을 합성하였다. 또한 구축된 저분자 화합물 라이브러리의 분자다양성을 극대화하기 위해서 nitrophenyl, anilyl, pyridyl 구조를 접목함으로서 polar surface area 와 중심골격을 3 차원 공간상에서 효율적으로 다양화하였으며, 이것은 계산화학적 접근을 통해서 증명되었다. 결과적으로 162 개의 새로운 의약유사 저분자 화합물 라이브러리를 구축하였으며 최종생성물은 추가적인 정제과정 없이 92%의 순도로 합성되었다.

Results and Discussion

Tetrahydroindazolones have been generally obtained through the simple condensation of 2-acylcyclohexane-1,3-dione (**3**) with substituted hydrazine, but the regioselectivity of this synthetic method is limited by its narrow scope of acceptable hydrazine substrates (Scheme 1).[22] As reported in the literature, arylhydrazines **1** have been commonly used for the regioselective synthesis of 1-aryltetrahydroindazolones **4** because arylhydrazines have an adequate chemical property to control the regiochemistry: the terminal nitrogen atom of arylhydrazines **1** is more nucleophilic than its internal nitrogen atom because of the conjugation of lone-pair electrons at the internal nitrogen atom to the aromatic ring system. Therefore, 1-aryl-substituted tetrahydroindazolones **4** can be synthesized through the condensation of **3** and **1** without the formation of 2-aryl-substituted tetrahydroindazolones **5**.

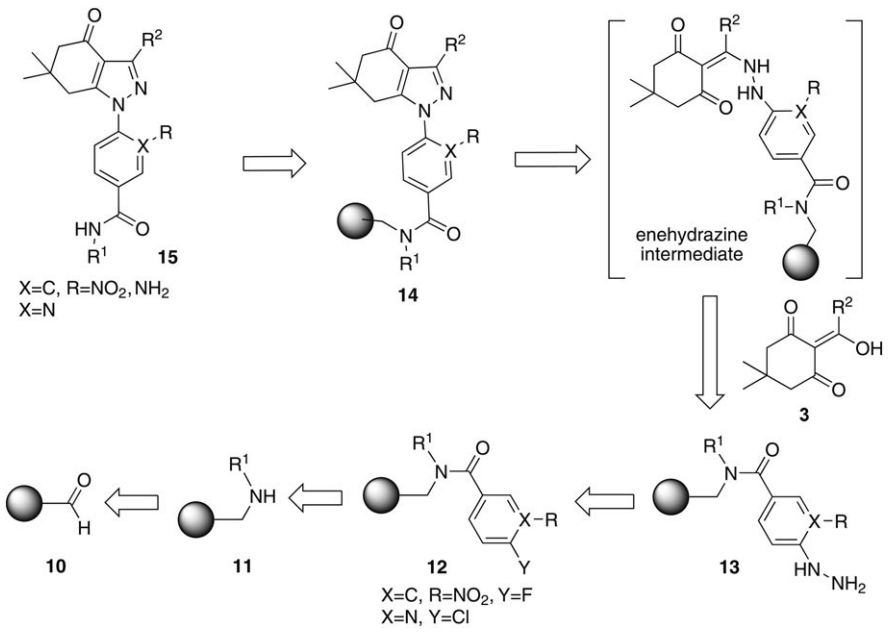
In contrast, the regioselective synthesis of alkyl-substituted tetrahydroindazolones cannot be achieved through condensation of **3** and alkylhydrzines **2** because of the similar nucleophilicities of the two nitrogen atoms in alkylhydrazines. To overcome this limitation, we previously developed a divergent strategy for the orthogonal synthesis of complementary regioisomers, 1-alkyl-3-substituted tetrahydro-indazolones (**6**) and 2-alkyl-3-substituted tetrahydroindazolones (**7**) from Boc-protected alkylhydrazines **8** (see Scheme 1).[23] The key feature of this strategy is the differentiation of nucleophilicity of two internal nitrogen atoms in alkylhydrazines through the selective protection of the internal nitrogen atom with a *tert*-butoxycarbonyl (Boc) group, which allows the selective formation of enehydrazines or intermediate **9** followed by the acid-catalyzed deprotecion of the Boc group and subsequent intra- or intermolecular cyclization. This divergent strategy fully controls the regioselective synthesis of *N*-alkyl-3-substituted tetrahydroindazolones. However, this novel synthetic method requires strongly acidic conditions under microwave irradiation, which are difficult to be applied for the practical construction of a drug-like small-molecule library containing tetrahydroindazolones when using a solid-phase parallel synthesis platform.

For the systematic construction of the tetrahydroindazolone library, we pursued the development of a divergent solid-phase parallel strategy through the robust condensation of arylhydrazines **13** immobilized on solid supports with various 2-acylcyclohexane-1,3-diones **3**. As shown in Scheme 2, we envisioned the usage of indole aldehyde resin as a suitable linker system because of the easy introduction of diversity elements for the library realization through the reductive amination of commercially available primary amines. Along with that, final products can be liberated from the solid support under mild acidic conditions when using 1% TFA in dichloromethane, thus the purity of final



Scheme 1. a) General syntheses of tetrahydroindozolones involve (left) the condensation of **1** and **3** to form 1-aryl-3-substituted tetrahydroindazolones **4** with good regioselectivity, and (right) the condensation of alkylhydrazines **2** with **3** to form *N*-alkyl-3-substituted tetrahydroindazolones **6** and **7** with no regioselectivity. b) Orthogonal regioselective synthesis of *N*-alkyl-3-substituted tetrahydroindazolones **6** and **7** using Boc-protected alkyl hydrazines **8**.[23] Boc = *tert*-butoxycarbonyl.

products can be enhanced through the minimized decomposition upon acid-catalyzed cleavage from solid supports.



Scheme 2. Regioselective solid-phase parallel synthetic strategy for the construction of a tetrahydroindazolone library.

Furthermore, we aimed to construct three discrete core skeletons to maximize the molecular diversity in the resulting collection of tetrahydroindazolones. Based on the synthetic strategy, we ensure the regioselectivity of the resulting tetrahydroindazolones through the usage of arylhydrazines, generated by the nucleophilic aromatic substitution of electron-deficient aromatic rings on solid supports with free hydrazine. On the basis of our preliminary studies, 1-fluoro-2-nitroaryl and 2-chloropyridyl moieties were suitable substrates for the formation of aryl- and heteroarylhydrazines. The resulting aryl- and heteroarylhydrazines were directly utilized for the regioselective construction of tetrahydroindazolones by condensation with various 2-acylcyclohexane-1,3-diones **3**. In addition, the resulting tetrahydroindazolones containing a nitro group can be transformed into the aniline moiety through $SnCl_2$-assisted reduction on solid supports. Therefore, we can robustly access the three unique core skeletons with a tetrahydroindazolone-based molecular framework. We then performed the in silico analysis to visualize the molecular diversity of the resulting three core skeletons. As shown in Figure 1, three representative compounds **16**, **17**, and **18** have a unique display of polar surface charges on the similar molecular frameworks. In fact, the polar surface area (PSA) and the distribution of polar surface charges are closely linked to noncovalent interactions, such as hydrogen bonding, ionic bonding, van der Waals forces, and hydrophobic interactions, for specific recognition of small-molecule ligands with various biopolymers. The unique display of polar surface charges on similar molecular frameworks was achieved through the introduction of dis-

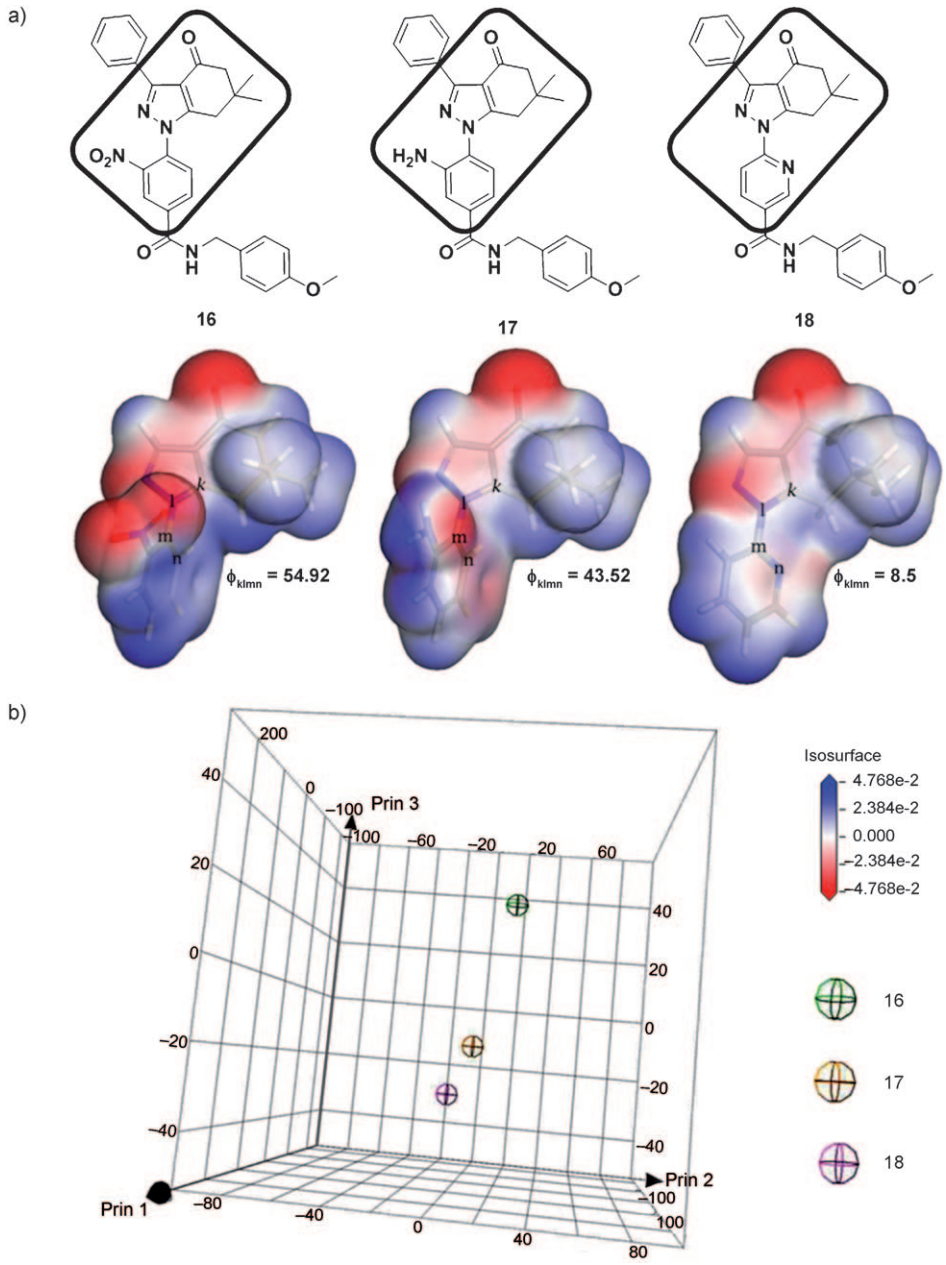
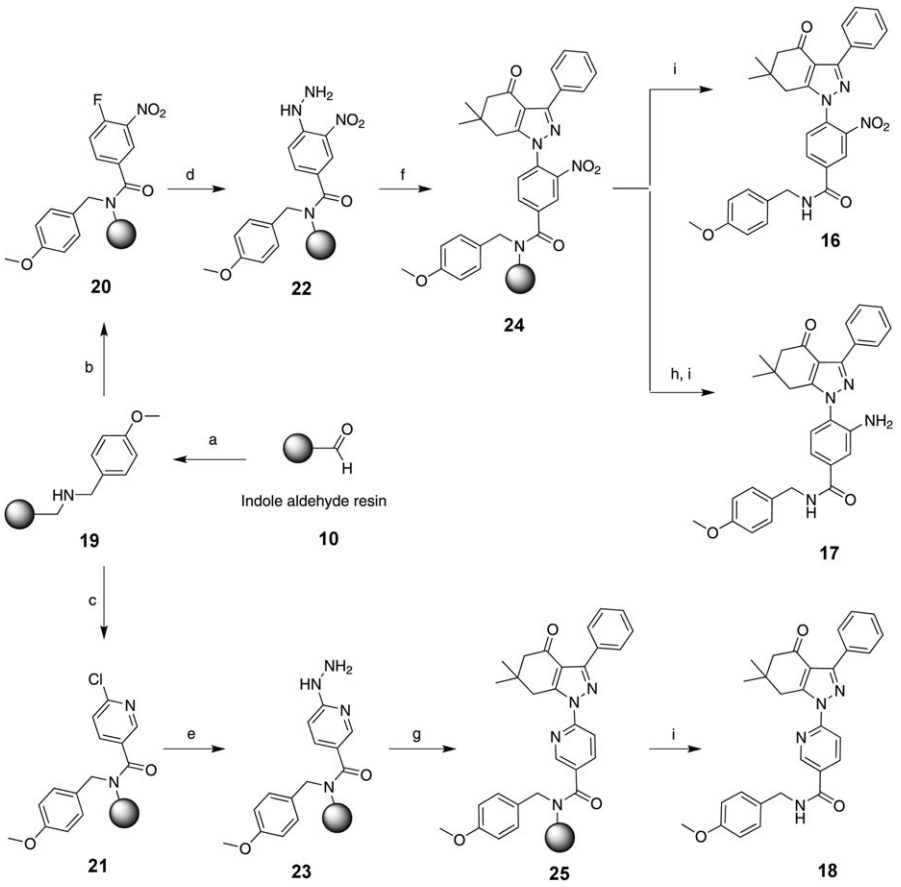


Figure 1. a) The PSA is illustrated by an isosurface diagram after an electrostatic potential and electron density calculation and the energy-minimized conformers of representative compounds **16**, **17**, and **18**. b) PCA of representative compounds **16**, **17**, and **18**.

similar moieties to common scaffolds, which was illustrated by an isosurface diagram after calculation of electrostatic potential and electron density. In addition, the actual trajectory of three different molecular frameworks with the nitrophenyl (**16**), anilyl (**17**), and pyridyl (**18**) moiety is dissimilar in 3D space and has quite different dihedral angles of the heterobiaryl junction (Φ_{klmn} = 54.9, 43.5, and 8.5°, respectively) because of intramolecular hydrogen bonding and steric interactions on the basis of our energy-minimized conformational analysis (see Figure 1a). The computational analysis with 15 discrete molecular descriptors and subsequent principle component analysis (PCA) clearly demonstrated that three representative compounds (**16**, **17**, and **18**) with three unique core skeletons containing tetrahydroindazolones are populated differently in the chemical space with maximized molecular diversity (see Figure 1b). By use of calculation data, we noticed that the Prin3 factor was the most important element related to PSA character from among three major principle components. Thus, three representative compounds were effectively differentiated in 3D chemical space by Prin3 and the resulting small-molecule library containing these scaffolds might induce the specific interactions with various biopolymers and facilitate the discovery of novel small-molecule modulators, which is the crown jewel of chemical biology.

The practical and divergent procedures for regioselective synthesis of tetrahydroindazolones in solid-phase parallel fashion were optimized through the preparation of representative tetrahydroindazolones containing nitrophenyl (**16**), anilyl (**17**), and pyridyl moiety (**18**). The reaction progress on solid supports was monitored in each step by using LCMS after cleavage from the solid support in combination with the on-bead colorimetric method. For direct comparison of each synthetic route, R^1 and R^2 were fixed with 4-methoxybenzyl and a phenyl group, respectively. As shown in Scheme 3, the synthesis was initiated by the incorpoartion of 4-methoxybenzylamine to indole aldehyde resin **10** through the reductive amination in the presence of TMOF in anhydrous THF and the subsequent treatment of sodium cyanoborohydride ($NaCNBH_3$) in acetic acid at room temperature.[24] The resin-bound secondary amine (**19**) was coupled with 4-fluoro-3-nitrobenzoic acid or 6-chloronicotinic acid through activation with HATU, which allows the introduction of nitrophenyl and pyridyl moiety to tetrahydroindazolones. After the completion of the amidation step, confirmed by a negative chloranil test, the resulting electron-deficient 4-fluoro-3-nitrophenyl (**20**) and 6-chloropyridyl (**21**) com-



Scheme 3. Solid-phase parallel synthesis of three representative compounds **16**, **17**, and **18** with three unique core skeletons containing tetrahydroindazolone: a) 4-methoxybenzyl amine, TMOF, THF, RT, 4 h, then $NaCNBH_3$, AcOH, RT, 2 h; b) 4-fluoro-3-nitrobenzoic acid, HATU, DIPEA, DMF, RT, 12 h; c) 6-chloronicotinic acid, HATU, DIPEA, DMF, RT, 12 h; d) hydrazine monohydrate, DMF, RT, 12 h; e) hydrazine monohydrate, pyridine, 100 °C, 12 h; f) 2-benzoyl-5,5-dimethylcyclohexane-1,3-dione, DMF, microwave, 100 °C, 30 min; g) 2-benzoyl-5,5-dimethylcyclohexane-1,3-dione, DMF, 60 °C, 12 h; h) 1 M $SnCl_2{\cdot}(H_2O)_2$ in DMF, 30 °C, 12 h; i) 1 % TFA in CH_2Cl_2, RT, 4 h. DIPEA = *N*,*N*-diisopropylethylamine, HATU = *O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyl uronium PF_6, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMOF = trimethyl orthoformate, DMF = *N*,*N*-dimethylformamide.

pounds on solid supports were treated with free hydrazine (NH_2NH_2) in DMF at room temperature or in pyridine at 100 °C to furnish the in situ generation of the corresponding nitrophenyl- (**22**) and pyridylhydrazine (**23**) on solid supports by nucleophilic aromatic *ipso*-substitution.

For the transformation of nitrophenylhydrazine **22** or pyridylhydrazine **23** to tetrahydroindazolones **24** or **25**, respectively, we screened the reaction conditions by changing various solvents, additives, and reaction temperatures (data not shown). In the case of pyridylhydrazine **23**, we obtained the desired tetrahydroindazolone **18** with high purity and yield in DMF at 60 °C followed by acid-catalyzed cleavage from solid supports by using 1 % TFA in dichloromethane. However, in the case of nitrophenylhydrazine **22**, the full conversion of the enehydrazine intermediate to the desired tetrahydroindazolone **16** cannot be achieved at 60 °C or even at a higher temperature in DMF, because of the significant reduction in the nucleophilicity of the internal amine on nitrophenylhydrazine **22** by the electron-withdrawing effect of the nitro group on the aryl ring. The further screening of reaction conditions allows the complete cyclization of nitroarylhydrazine **22** with 2-benzoyl-5,5-dimethylcyclohexane-1,3-dione at 100 °C in DMF with microwave irradiation. Finally, we transformed the nitro group on resin-bound tetrahydroindazolone **24** to anilyl moiety **17** by selective reduction with 1 M tin(II) chloride dihydrate in DMF at 30 °C. As shown in Scheme 3, the representative compounds **16**, **17**, and **18** were achieved upon treatment of 1 % TFA in dichloromethane for acidolysis from solid support in excellent purities (> 90 %) without further purification.

After the confirmation of molecular diversity in three unique core skeletons and the optimization of the solid-phase synthetic procedure, we pursued the construction of the tetrahydroindazolone pilot library containing three core skeletons by using various commercially available primary amines as the R^1 diversity elements and in-house prepared 2-acylcyclohexane-1,3-diones **3** as the R^2 diversity elements. To ensure the quantity of final products, we used 50 mg of indole aldehyde resins per library member and the optimized reaction conditions yielded 5–20 mg of final products after acid-catalyzed cleavage from solid support without further purification. In the cases of [3-(trifluoromethyl)phenyl]methanamine (R^1 = g) or 5,5-dimethyl-2-[4-(trifluoromethyl)benzoyl]cyclohexane-1,3-dione (R^2 = 6), we observed the significant retardation in the intramolecular nucleophilic cyclization of enehydrazine intermediates to the desired tetrahydroindazolones, probably due to the decreased nucleophilicity of hydrazine. Thus, the condensation reactions with these particular substrates were carried out at a higher temperature (X = C, R = NO_2, or NH_2, microwave irradiation at 110 °C; X = N, 80 °C) than in the optimized conditions to complete the cyclization. As shown in Tables 1 and 3, the drug-like small-molecule pilot library containing 1-nitrophenyl-3-substituted tetrahydroindazolones **30**{R^1,R^2} and 1-pyridyl-3-substituted tetrahydroindazolones **36**{R^1,R^2} was synthesized in an overall five steps with nine primary amines (a–i) at the R^1 position and seven substituents (1–7) of 2-acylcyclohexane-1,3-diones **3** at the R^2 position. Under

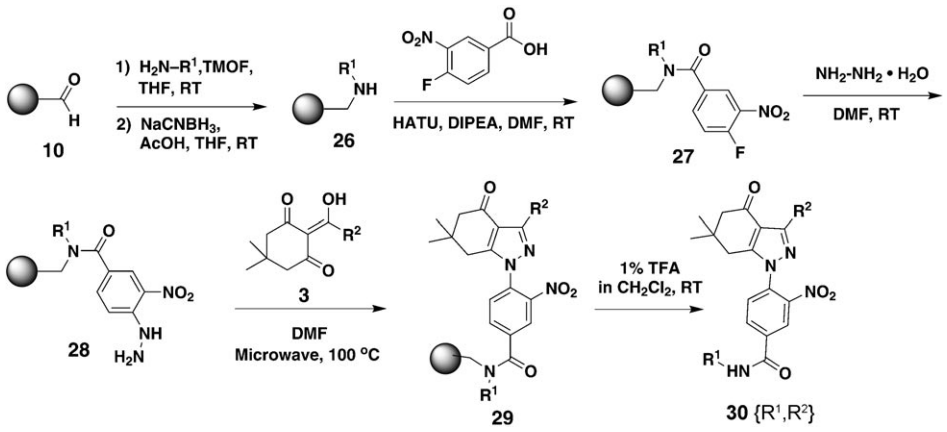
the library-to-library concept from **30**{R^1,R^2} to **32**{R^1,R^2}, the nitrophenyl-substituted core skeleton (**29**) was transformed to anilyl-substituted tetrahydroindazolones (**31**) on solid support upon treatment of 1 M $SnCl_2$ in DMF at 30 °C. In fact, the average purity of the resulting **32**{R^1,R^2} is much lower than **30**{R^1,R^2}, especially with substrates containing simple alkyl or tetrahydrofuranyl moieties at the R_1 position, probably because of its harsh reduction conditions. Therefore, the pilot library containing **32**{R^1,R^2} was constructed by using fewer building blocks than those with **30**{R^1,R^2} and **36**{R^1,R^2}. The purities and identities of all the library members were assessed by the direct analysis of crude final products by using LCMS. The presence of all the desired compounds was unambiguously confirmed by the molecular weight with an excellent purity range, as determined by the HPLC analysis by using a photodiode array (PDA) detector. The purity of each library member containing three unique core skeletons (**30**, **32**, and **36**) is labeled with different colors in Tables 1, 2, and 3, respectively. The average purity of final crude products was 92 (**30**, X = C, R = NO_2, see Scheme 2), 91 (**32**, X = C, R = NH_2), and 93% (**36**, X = N). The representative final crude products of the tetrahydroindazolone library were fully characterized by ^{1}H and ^{13}C NMR spectroscopy along with LCMS analysis (see Table 4 and the Supporting Information).

To visualize the importance of three unique core skeletons (**30**, **32**, and **36**) along with the maximized molecular diversity of the resulting tetrahydroindazolone library, all of the library members were subjected to the calculation with fifteen major molecular descriptors by using PreADMET (BMDRC, Seoul, Korea). Through the orthogonal linear transformation of fifteen molecular descriptors to a new matrix by using SAS 9.1 (SAS Institute, Cary, NC), the dimensionality of diversity matrix with fifteen orthogonal principal components was reduced down to a 3D coordiante system for visualizing the molecular diversity in chemical space with three major principal components. Three principal components (Prin1, Prin2, and Prin3) represent 97.0% of the total variance in molecular descriptors. The Prin1 factor, which explains 81.3% of the total variance, is mainly constituted by molecular weight (MW), van der Waals (VDW) surface, and VDW volume. The Prin2 factor, which explains 10.5% 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 5.3% of the total variance, includes hydrogen-bond acceptor surface area, polar VDW surface area, and topological polar surface area (see the Supporting Information). As shown in Figure 2, each library member containing different core skeletons (**30**, **32**, and **36**) with different color codes (red, yellow, and blue) are distributed in the different regions of 3D chemical space, thus the molecular diversity of the resulting small-molecule library is effectively maximized through the introduction of tetrahydroindazolone-based three unique core skeletons.

Conclusions

In this study, we developed the practical and divergent strategy for the regioselective synthesis of a 3-substituted tetrahydroindazolone library. Even though we previously report-

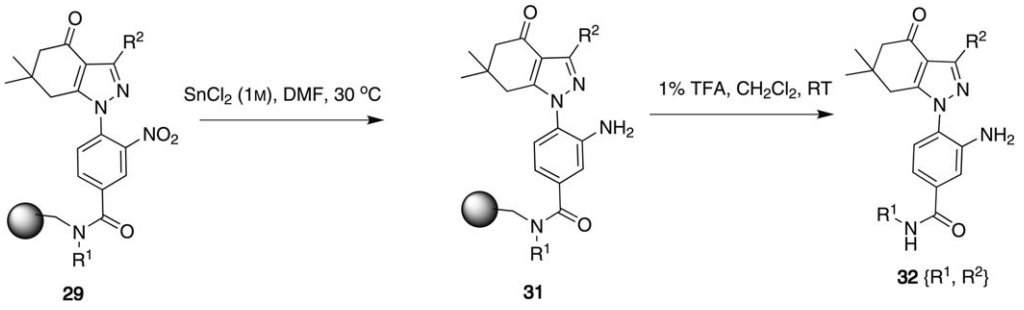
Table 1. Set of building blocks and purities [%] of tetrahydroindazolones **30**.[a]



	30 {R^1,R^2}	R^1									
			a	b	c	d	e	f	g	h	i
R^2	methyl	1	95	99	97	95	80	94	98	93	98
	phenyl	2	90	91	93	90	90	94	97	97	91
	furan-2-yl	3	90	85	87	71	90	84	86	73	95
	3,4-dimethoxybenzyl	4	90	94	93	92	93	93	93	99	92
	but-3-enyl	5	90	95	96	90	84	90	99	97	95
	4-trifluoromethylpheny	6	93	92	90	95	95	96	99	95	94
	isobutyl	7	86	77	86	88	96	82	90	97	93

[a] Purities were obtained by PDA-based LCMS analysis of final products without further purification.

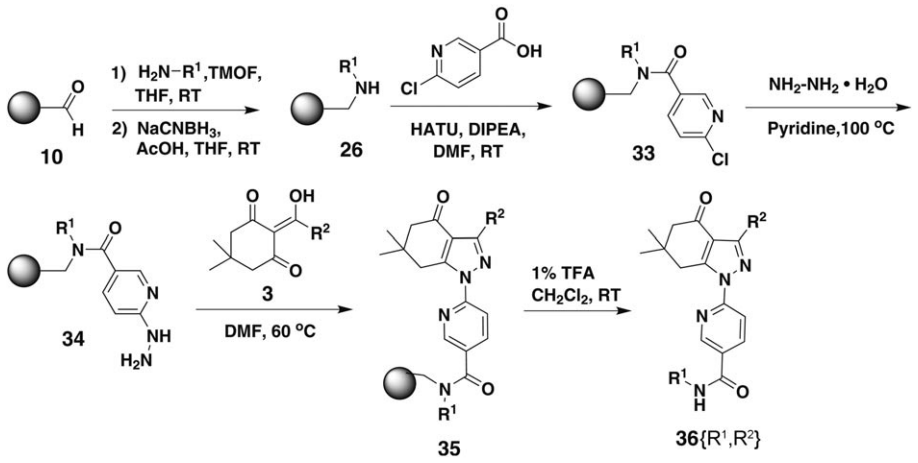
Table 2. Set of building blocks and purities [%] of tetrahydroindazolones **32**.[a]



	32 {R^1,R^2}	R^1	a	b	c	d	e	f
	methyl	1	92	90	94	87	98	92
	phenyl	2	90	87	84	81	96	93
R^2	3,4-dimethoxybenzyl	3	90	91	95	90	95	90
	but-3-enyl	4	90	90	93	92	97	92
	4-trifluoromethylpheny	5	90	91	94	90	96	92
	furan-2-yl	6	95	81	94	94	90	92

[a] Purities were obtained by PDA-based LCMS analysis of final products without further purification.

Table 3. Set of building blocks and purities [%] of tetrahydroindazolones **36**.[a]



	36 {R^1,R^2}	R^1	a	b	c	d	e	f	g	h	i
	methyl	1	83	99	97	95	93	94	99	90	90
	phenyl	2	98	96	90	99	92	91	99	92	95
R^2	furan-2-yl	3	94	93	98	90	97	98	91	78	90
	3,4-dimethoxybenzyl	4	90	91	88	92	90	92	94	90	86
	but-3-enyl	5	85	97	92	96	82	93	94	88	91
	4-trifluoromethylpheny	6	96	99	99	99	99	97	85	91	92
	isobutyl	7	93	96	95	98	94	94	99	90	91

[a] Purities were obtained by PDA-based LCMS analysis of final products without further purification.

ed the orthogonal synthesis of complementary regioisomers, 1-alkyl-3-substituted (**6**) and 2-alkyl-3-substituted tetrahydroindazolones (**7**) from Boc-protected alkylhydrazines **8**, we pursued the regioselective synthesis of 1-(hetero)aryl-3-substituted tetrahydroindazolone through simple condensation of (hetero)arylhydrazine (**12**) on solid supports with 2-acylcyclohexane-1,3-diones **3** to ensure the efficiency of our solid-phase parallel synthetic strategy. In addition, we have overcome the existing drawback of this condensation reaction through the introduction of three unique core skeletons

Table 4. Purity and mass confirmation of representative compounds in the tetrahydroindazolone library.

Compound	R^1	R^2	Purity [%]	MS $[M+H]^+$	
				calcd	obs
30{a,1}	benzyl	methyl	95	433.18	432.92
30{b,2}	2-methoxy-ethyl	phenyl	91	463.19	463.00
30{i,4}	tetrahydro-furan-2-yl	3,4-dimethoxy-benzyl	93	563.24	563.14
32{d,3}	4-mehtyl-phe-nethyl	3,4-dimethoxy-benzyl	90	567.29	567.25
36{a,3}	benzyl	furan-2-yl	94	441.18	441.12
36{b,5}	2-methoxy-ethyl	but-3-enyl	97	397.22	397.09

with a different display of polar surface area. In this procedure, two different arylhydrazines were in situ generated on solid supports after the introduction of the first diversity element at the R^1 position and subjected to the regioselective intramolecular condensation with various 2-acylcyclohexane-1,3-diones **3**. We also applied the library-to-library concept for the further diversification of core skeletons by $SnCl_2$-based solid-phase reduction. The resulting tetrahydroindazolone-based core skeletons (**30**, **32**, and **36**) occupy the different regions of 3D chemical space because of their unique display of polar surface area, a new diversity element, along with different dihedral angles of heterobiaryl skeletons. The optimized synthetic procedures were tolerant toward various building blocks and the 162-membered tetrahydroindazolone library was constructed in parallel with 92% average purity. The biological evaluation of the library members will be reported in due course.

Experimental Section

General

All commercially available reagents and solvents were used without further purification unless noted otherwise. All the solvents were purchased from commercial venders. Indole aldehyde resin was obtained from Novabiochem. ^1H and ^{13}C NMR spectra were obtained on a Varian Inova-500 (Varian Assoc., Palo Alto, USA). Chemical shifts were reported in ppm from tetramethylsilane (TMS) as the internal standard or the residual solvent peak ($CDCl_3$, ^1H: $\delta = 7.26$, ^{13}C: 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 doublets), brs (broad singlet), etc. Coupling constants are reported in hertz. The reaction steps for library construction were performed in parallel by using the FlexChem Synthesis System from SciGene (Sunnyvale, CA) in a 96-deep-well filtration block. The purity of all the library members was observed by a LCMS system equipped with a reverse-phase column (C-18, 50×2.1 mm, 5 μm) and photodiode array (PDA) detector by using electron spray ionization (ESI). Microwave reactions were performed by using a CEM Discover Benchmate and microwave reaction conditions were denoted in the Experimental Section. Yields of crude products were calculated on the basis of the loading amount of primary amines on the solid support. Purities of final crude products were analyzed by LCMS equipped with a PDA detector without further purification.

Typical Solid-Phase Reaction Procedures. Step 1: Reductive Amination[24]

Individual wells of a 96-deep-well filtration block were loaded with indole aldehyde resin **10** (50 mg, loading level: 0.9 mmol g^{-1}, 0.045 mmol). R_1-amines (2.2 equiv, 0.099 mmol) in a cosolvent of THF (0.25 mL) and trimethyl orthoformate (TMOF, 0.25 mL) were dispensed into the designated wells of the reaction block. The reaction mixture was shaken at room temperature in a rotating oven (Robbins Scientific) for 4 h. Then, a solution of $NaCNBH_3$ (2.2 equiv, 0.099 mmol) in AcOH (0.01 mL) and THF (0.10 mL) were added to the reaction block. The reaction mixture was shaken at room temperature in a rotating oven for 2 h. The resulting resins **26** were washed with DMF, MeOH, and CH_2Cl_2 sequentially (×3 each) and dried in vacuo.

Step 2: Acid Coupling

A reaction cocktail of 4-fluoro-3-nitrobenzoic acid (3 equiv) or 6-chloronicotinic acid (3 equiv), HATU (3 equiv), and DIPEA (6 equiv) in DMF (1.3 mL) was dispensed into each well of the reaction block charged with resins **26**. The reaction mixture was incubated in a rotating oven at room temperature for 12 h. The resins were then washed extensively with DMF, MeOH, and CH_2Cl_2 (×3 each) and dried in vacuo. The reaction completion was confirmed by a negative chloranil test.

*Step 3a: Nucleophilic Aromatic Substitution for the Preparation of **28***

A solution of hydrazine monohydrate (20 equiv) in DMF (1.3 mL) was added to a designated well charged with resins **27**. The reaction mixture was shaken at room temperature in a rotating oven for 12 h. The resins were then washed (×3) with DMF, MeOH, and CH_2Cl_2 and dried in vacuo.

*Step 3b: Nucleophilic Aromatic Substitution for the Preparation of **34***

A solution of hydrazine monohydrate (20 equiv) in pyridine (1.3 mL) was added to a designated well charged with resins **33**. The reaction mixture was shaken at 100 °C in a rotating oven for 12 h. The resins were then washed (×3) with DMF, MeOH, and CH_2Cl_2 and dried in vacuo.

*Step 4a: Cyclization for the preparation of **29***

2-Acylcyclohexane-1,3-diones **3** (3 equiv) were added to a designated resins **28** in DMF (1.3 mL), and the reaction mixture was heated in a capped microwave vessel under microwave irradiation (150 W, 100 °C or 110 °C) for 25–30 min. The resin was filtered, washed (×3) with DMF, MeOH, and CH_2Cl_2, and then dried in vacuo.

*Step 4b: Cyclization for the Preparation of **35***

A solution of 2-acylcyclohexane-1,3-diones **3** (3 equiv) in DMF (1.3 mL) was added to each well charged with resins **34**. The reaction mixture was incubated in a rotating oven at 60 or 80 °C for 12 h. The resins were then washed extensively with DMF, MeOH, and CH_2Cl_2 (×3 each) and dried in vacuo.

Step 5: Reduction of the Nitro Group

The aromatic nitro group of resin **29** was reduced to aniline upon treatment with 1 M $SnCl_2{\cdot}(H_2O)_2$ in DMF (1.3 mL) at 30 °C for 12 h, followed by washing (×3) with DMF, MeOH, and CH_2Cl_2. The resulting resin was dried in vacuo.

Step 6: Acid-Catalyzed Cleavage

After the resulting resins in the 96-deep-well reaction blocks were dried under high vacuum, resins were treated with 1% TFA in CH_2Cl_2 at room temperature for 4 h. Then, the resins were removed by filtration and washed several times with CH_2Cl_2. The filtrate was condensed under reduced pressure by using GeneVac (Thermo Savant) and the resulting residues were diluted with 50% H_2O/ACN and freeze-dried, which yielded final products as a pale-yellow powder. The purity of the final products was confirmed by LC/MS without further purification.

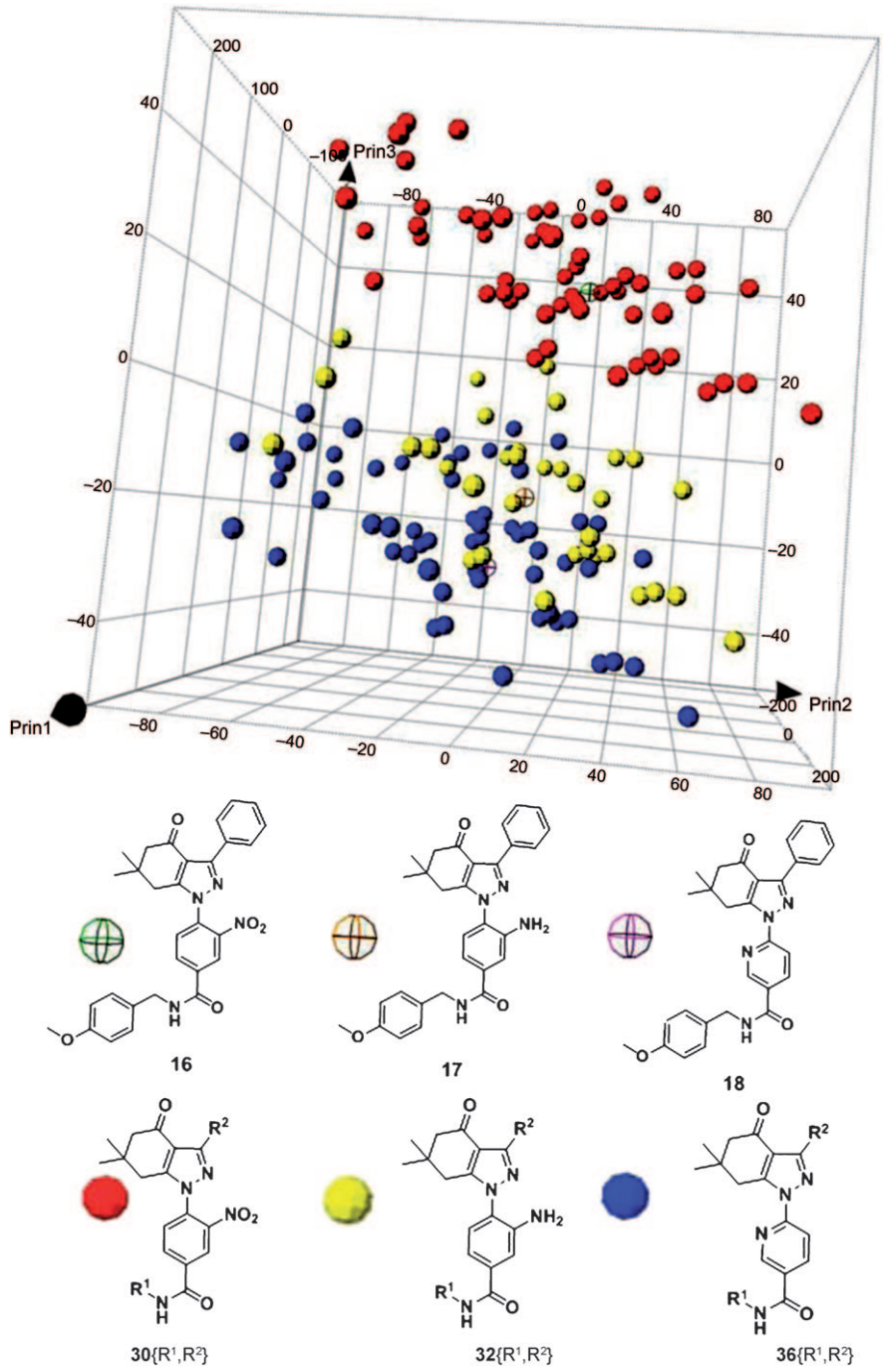


Figure 2. PCA of representative compounds (**16**, **17**, and **18**) and chemsets (**30**, **32**, and **36**) containing three unique tetrahydroindazolone core skeletons.

Characterization of Representative Compounds. Compound ***16***

Yield: 63%; purity: 93%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.37 (d, J=1.5 Hz, 1H), 8.18 (dd, J=8.0, 1.5 Hz, 1H), 7.97 (t, J=3.5 Hz, 2H), 7.58 (brs, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.47–7.45 (m, 3H), 7.21 (d, J=7.5 Hz, 2H), 6.83 (d, J=7.5 Hz, 2H), 4.49 (d, J=5.0 Hz, 2H), 3.76 (s, 3H), 2.53 (s, 2H), 2.39 (s, 2H), 1.06 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=192.5, 164.1, 159.3, 152.9, 152.7, 145.6, 136.6, 133.5, 132.5, 131.2, 129.7, 129.53, 129.49, 129.0, 128.3, 124.4, 116.1, 114.3, 55.5, 53.2, 44.0, 36.2, 35.7, 28.2 ppm; MS (ESI+): m/z: calcd for $C_{30}H_{29}N_4O_5$: 525.21 $[M+H]^+$; found: 525.02.

Compound ***17***

Yield: 58%; purity: 93%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.28 (brs, 2H), 8.04 (dd, J=7.3, 1.8 Hz, 2H), 7.41–7.38 (m, 3H), 7.31 (s, 1H), 7.22 (d, J=8.5 Hz, 2H), 7.18 (br t, J=5.0 Hz, 1H), 7.13 (d, J=8.5 Hz, 1H), 7.09 (d, J=8.5 Hz, 1H), 6.85 (d, J=8.5 Hz, 2H), 4.48 (d, J=5.0 Hz, 2H), 3.77 (s, 3H), 2.59 (s, 2H), 2.43 (s, 2H), 1.07 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=193.5, 168.0, 159.4, 153.0, 152.7, 142.2, 135.8, 131.1, 129.7, 129.5, 129.0, 128.4, 127.9, 127.1, 126.4, 117.3, 117.1, 115.3, 114.3, 55.4, 53.0, 44.1, 36.4, 35.4, 28.2 ppm; MS (ESI+): m/z: calcd for $C_{30}H_{31}N_4O_3$: 495.23 $[M+H]^+$; found: 495.10.

Compound ***18***

Yield: 68%; purity: 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.87 (s, 1H), 8.22 (d, J=8.0 Hz, 1H), 8.13 (d, J=8.5 Hz, 1H), 8.09 (d, J=6.5 Hz, 2H), 7.43 (brd, J=7.5 Hz, 2H), 7.29 (d, J=7.5 Hz, 2H), 6.89 (d, J=7.5 Hz, 2H), 6.70 (brs, 1H), 4.58 (d, J=4.0 Hz, 2H), 3.80 (s, 3H), 3.39 (s, 2H), 2.46 (s, 2H), 1.16 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=193.3, 164.9, 159.5, 154.6, 152.6, 152.5, 147.0, 137.8, 131.6, 129.8, 129.6, 129.5, 129.3, 128.3, 128.2, 117.7, 115.5, 114.4, 55.5, 53.3, 44.0, 39.7, 35.2, 28.7 ppm; MS (ESI+): m/z: calcd for $C_{29}H_{29}N_4O_3$: 481.22 $[M+H]^+$; found: 481.11.

Compound ***30{a,1}***

Yield: 67%; purity: 95%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.42 (d, J=1.5 Hz, 1H), 8.18 (dd, J=8.5, 2.0 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.38–7.31 (m, 5H), 7.02 (brt, J=5.3 Hz, 1H), 4.66 (d, J=6.0 Hz, 2H), 2.52 (s, 2H), 2.47 (s, 3H), 2.38 (s, 2H), 1.09 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=193.4, 164.0, 151.7, 151.5, 145.8, 137.5, 136.4, 134.0, 132.4, 129.4, 129.2, 128.3, 128.2, 124.3, 117.3, 52.5, 44.8, 36.2, 36.0, 28.4, 13.5 ppm; MS (ESI+): m/z: calcd for $C_{24}H_{25}N_4O_4$: 433.18 $[M+H]^+$; found: 432.92.

Compound ***30{b,2}***

Yield: 63%; purity: 91%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.42 (d, J=1.5 Hz, 1H), 8.17 (dd, J=8.5, 2.0 Hz, 1H), 8.02 (dd, J=8.5, 2.0 Hz, 2H), 7.60 (d, J=8.0 Hz, 1H), 7.43–7.38 (m, 3H), 7.01 (brt, J=5.3 Hz, 1H), 3.70 (q, J=5.1 Hz, 2H), 3.60 (t, J=5.3 Hz, 2H), 2.59 (s, 2H), 2.48 (s, 2H), 1.11 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=192.4, 164.3, 153.1, 152.7, 145.9, 136.7, 133.8, 132.3, 131.2, 129.5, 129.3, 129.1, 128.3, 124.4, 116.2, 70.9, 59.1, 53.3, 40.4, 36.4, 35.8, 28.3 ppm; MS (ESI+): m/z: calcd for $C_{25}H_{27}N_4O_5$: 463.19 $[M+H]^+$; found: 463.00.

Compound ***30{i,4}***

Yield: 69%; purity: 93%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.43 (d, J=2.0 Hz, 1H), 8.15 (dd, J=8.3, 1.8 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 7.15

(brt, J=5.5 Hz, 1H), 6.90–6.86 (m, 2H), 6.75 (d, J=8.0 Hz, 1H), 4.18–4.12 (m, 3H), 3.93–3.88 (m, 1H), 3.86–3.79 (m, 7H), 3.37–3.31 (m, 1H), 2.56 (s, 2H), 2.38 (s, 2H), 2.11–2.06 (m, 1H), 1.96 (p, J=6.1 Hz, 2H), 1.65–1.59 (m, 2H), 1.08 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 193.5, 164.5, 154.3, 152.1, 148.8, 147.6, 146.1, 136.4, 133.7, 132.2, 130.9, 129.0, 124.5, 121.2, 116.6, 112.3, 111.1, 77.9, 68.5, 55.9, 52.4, 44.5, 36.2, 36.0, 33.2, 29.0, 28.4, 25.9 ppm; MS (ESI+): m/z: calcd for $C_{30}H_{35}N_4O_7$: 563.24 $[M+H]^+$; found: 563.14.

Compound ***32{d,3}***

Yield: 57%; purity: 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.52 (brs, 2H), 7.14–6.99 (m, 8H), 6.92 (d, J=8.0 Hz, 1H), 6.75 (d, J=8.5 Hz, 1H), 6.49 (brs, 1H), 4.22 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.68 (q, J=5.8 Hz, 2H), 2.88 (t, J=6.5 Hz, 2H), 2.58 (s, 2H), 2.41 (s, 2H), 2.33 (s, 3H), 1.07 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=194.9, 168.3, 154.1, 152.5, 148.8, 147.7, 136.6, 135.7, 135.2, 131.0, 129.6, 128.7, 126.9, 121.2, 117.6, 116.2, 115.7, 114.0, 112.6, 111.4, 55.9, 52.2, 42.0, 36.0, 34.9, 33.0, 32.1, 28.3, 21.1 ppm; MS (ESI+): m/z: calcd for $C_{34}H_{39}N_4O_4$: 567.29 $[M+H]^+$; found: 567.32.

Compound ***36{a,3}***

Yield: 65%; purity: 94%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.89 (d, J= 2.0 Hz, 1H), 8.23 (dd, J=8.5, 2.5 Hz, 1H), 8.14 (d, J=8.5 Hz, 1H), 7.90 (d, J=3.8 Hz, 1H), 7.55 (d, J=1.5 Hz, 1H), 7.37–7.30 (m, 5H), 6.74 (brs, 1H), 6.53 (dd, J=3.5, 2.0 Hz, 1H), 4.66 (d, J=5.5 Hz, 2H), 3.36 (s, 2H), 2.47 (s, 2H), 1.15 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=192.7, 164.9, 154.4, 152.2, 147.0, 146.4, 143.6, 143.1, 137.8, 137.8, 129.1, 128.3, 128.2, 128.1, 116.8, 115.8, 115.2, 111.9, 53.0, 44.5, 39.5, 35.1, 28.6 ppm; MS (ESI+): m/z: calcd for $C_{26}H_{25}N_4O_3$: 441.18 $[M+H]^+$; found: 441.12.

Compound ***36{b,5}***

Yield: 72%; purity: 97%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.85 (d, J= 2.0 Hz, 1H), 8.22 (dd, J=8.8, 2.3 Hz, 1H), 8.03 (d, J=9.0 Hz, 1H), 6.75 (brt, J=5.3 Hz, 1H), 5.93–5.86 (m, 1H), 5.06 (dq, J=17.3, 1.5 Hz, 1H), 4.95 (dq, J=9.8, 1.1 Hz, 1H), 3.67 (q, J=5.0 Hz, 2H), 3.58 (t, J=5.3 Hz, 1H), 3.39 (s, 3H), 3.31 (s, 2H), 3.03–3.00 (m, 2H), 2.52–2.49 (m, 2H), 2.37 (s, 2H), 1.12 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=194.1, 165.1, 154.6, 154.4, 151.6, 146.9, 138.1, 137.8, 127.8, 118.2, 115.2, 115.1, 71.1, 59.1, 52.6, 40.0, 39.5, 35.5, 32.3, 28.8, 27.5 ppm; MS (ESI+): m/z: calcd for $C_{22}H_{29}N_4O_3$: 397.22 $[M+H]^+$; found: 397.09.

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