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Emulating the Logic of Monoterpenoid Alkaloid Biogenesis to Access a Skeletally Diverse Chemical Library

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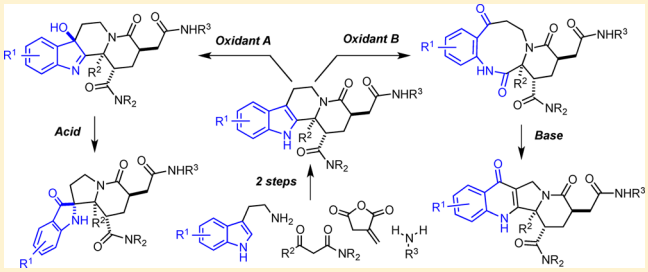
Supporting Information

ABSTRACT: We have developed a synthetic strategy that mimics the diversity-generating power of monoterpenoid indole alkaloid biosynthesis. Our general approach goes beyond diversification of a single natural product-like substructure and enables production of a highly diverse collection of small molecules. The reaction sequence begins with rapid and highly modular assembly of the tetracyclic indoloquinolizidine core, which can be chemoselectively processed into several additional skeletally diverse structural frameworks. The general utility of this approach was demonstrated by parallel synthesis of two representative chemical libraries containing 847 compounds with favorable physicochemical properties to enable its subsequent broad pharmacological evaluation.



INTRODUCTION

Secondary metabolism creates a diverse ensemble of natural products. The power of natural product biogenesis has stimulated the development of the field of combinatorial biosynthesis, which aims to generate new collections of molecules that resemble natural products.[1] However, because of the difficulty of re-engineering natural product biosynthesis pathways, such strategies have yielded only a limited number of new compounds. While a number of synthetic strategies to produce natural product-like libraries have been developed,[2] including biomimetic approaches,[3] they typically represent diversification of a specific natural product structure and provide limited skeletal diversity. Here we describe our design and execution of a synthetic strategy that reaches beyond diversification of a single natural product-like substructure and enables production of a collection of skeletally diverse small molecules for subsequent pharmacological probe discovery.

The divergent nature of monoterpenoid indole alkaloid biosynthesis provides a wide range of natural products based on two relatively simple precursors, including tryptamine **1a** and secologanin **2** (Figure 1A).[4] The initial condensation between **1a** and **2** entails a Pictet-Spengler cyclization to give strictosidine **3**.[5] Subsequent processing of this biosynthetic intermediate enables branching into several additional pathways. Deglycosidation, followed by intramolecular reductive amination and indole oxidation yields hydroxy indolenine **4**, which can rearrange into spirocyclic geissoschizine oxindole **5**.[6] Alternatively, strictosidine **3** can undergo lactamization, followed by putative oxidative cleavage of the indole moiety to give ketoamide **6**. Subsequent transannular cyclization produces pumiloside **7**, which is ultimately converted into camptothecin.[7] Such representative examples have demonstrated how changes in oxidation states at specific positions of a polycyclic molecular framework could lead to a highly controlled fragmentation and progressive diversification of a complex skeletal architecture. While recent studies demonstrate that such biosynthetic pathways could be attractive for the production of unnatural indole alkaloids, only a small number of new compounds have been prepared using this approach, either by feeding unnatural tryptamine derivatives or re-engineering the substrate specificity of biosynthetic enzymes.[8,9]

Our synthetic strategy to a skeletally diverse chemical library, which is reminiscent of monoterpenoid indole alkaloids, is depicted in Figure 1B. First, we aimed to develop an efficient and highly diastereoselective entry into a series of substituted indoloquinolizidines **10**, representing the skeletal branching point. Those compounds can be readily assembled starting with appropriate tryptamines **1**, 1,3-dicarbonyls **8** and itaconic anhydride **9**. The next challenge was to identify reaction conditions that would efficiently reshape polycyclic molecular architecture of **10** in the absence of biosynthetic enzymes. We considered a series of possible transformations of this key synthetic intermediate into other polycyclic skeletal frameworks via chemoselective oxidation of the indole moiety, which would induce subsequent controlled fragmentation of this tetracyclic core structure. Chemoselective oxidation at the C(7) could furnish hydroxyindoline **11**. Subsequent rearrangement of **11** would produce spirocyclic dihydroindolone **12**. Alternatively, oxidative cleavage of indoloquinolizidine **10** at the C(2)−C(7) bond would produce ring-opened ketoamide **13**, which could be further elaborated into quinolone **14** via transannular aldol reaction, followed by dehydration. This approach would deliver a chemical library containing multiple core structures, which

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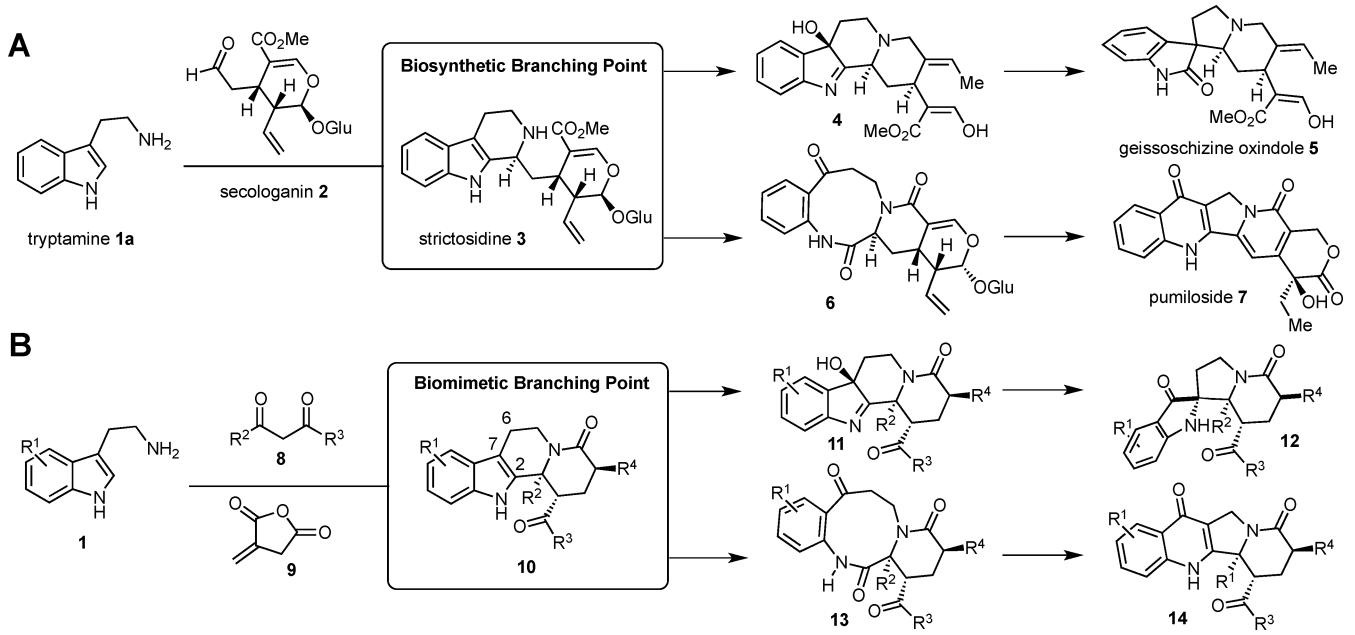


Figure 1. (A) Biosynthetic interconversions of representative monoterpenoid indole alkaloids via intermediacy of strictosidine **3**. (B) Synthetic strategy to a skeletally diverse chemical library via rapid assembly and subsequent transformations of indoloquinolizidine **10**, which served as a biomimetic branching point.

could be readily decorated at several positions providing rapid access to both skeletal and peripheral diversity.

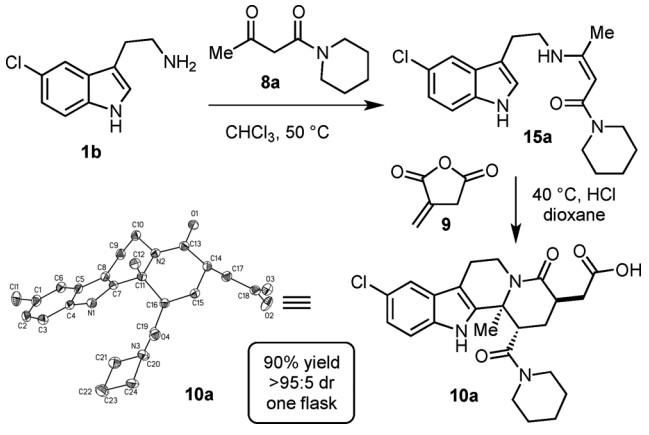
RESULTS AND DISCUSSION

We began our studies by examining construction of the indoloquinolizidine skeleton **10**. In order to rapidly assemble the tetracyclic molecular framework, we took advantage of the known propensity of vinylogous carbamates to undergo *N*-acyliminium ion cyclizations when subjected to either unsaturated acid chlorides or acid anhydrides.[10] Condensation of tryptamine **1b** with ketoamide **8a** gave the corresponding vinylogous urea **15a**, which was next treated with itaconic anhydride **9** to give indoloquinolizidine **10a** in 90% yield (Scheme 1). The relative stereochemistry of **10a** was established by X-ray crystallography. This process entailed a 1,4-addition of the vinylogous urea derived from **1b** and **8a** to a Michael acceptor **9**, followed by anhydride opening and *N*-acyliminium ion cyclization. Following solvent and temperature optimization studies, we found that this transformation proceeded with excellent diastereoselectivity when the reaction was conducted in 1,4-dioxane at 40 °C.

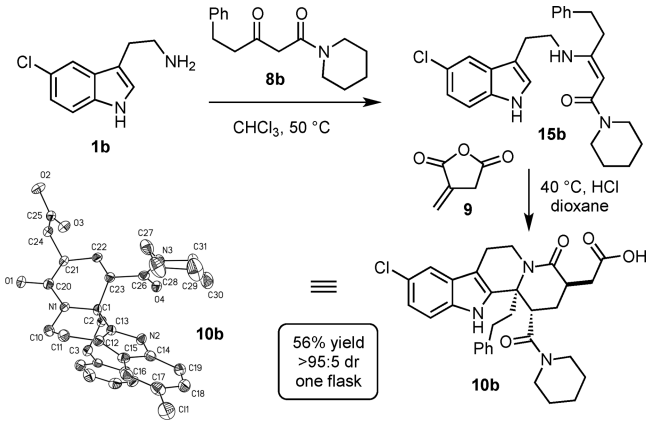
We next examined the generality of this transformation and found that a range of substituted tryptamines and 1,3-ketoamides can be successfully employed to produce the corresponding indoloquinolizidines in high yields and excellent diastereoselectivity. A representative example of these studies is shown in Scheme 2. Treatment of 5-chloro-tryptamine **1b** with ketoamide **8b** cleanly produced vinylogous urea **15b**, which was efficiently cyclized to afford indoloquinolizidine **10b** in a one-flask operation upon treatment with **9** and HCl in dioxane at 40 °C. The structure of **10b** was also confirmed by X-ray crystallography.

Having established a highly efficient and general indoloquinolizidine synthesis, we next examined its application to a larger set of compounds based on this tetracyclic platform (Figure 2). We prepared a 480-member library **17** starting with five tryptamines **1** and eight ketoamides **8** to deliver 40 indoloquinolizidine-containing carboxylic acids **10**. Each of

Scheme 1. One-Flask Synthesis of Indoloquinolizidine 10a



Scheme 2. One-Flask Synthesis of Indoloquinolizidine 10b



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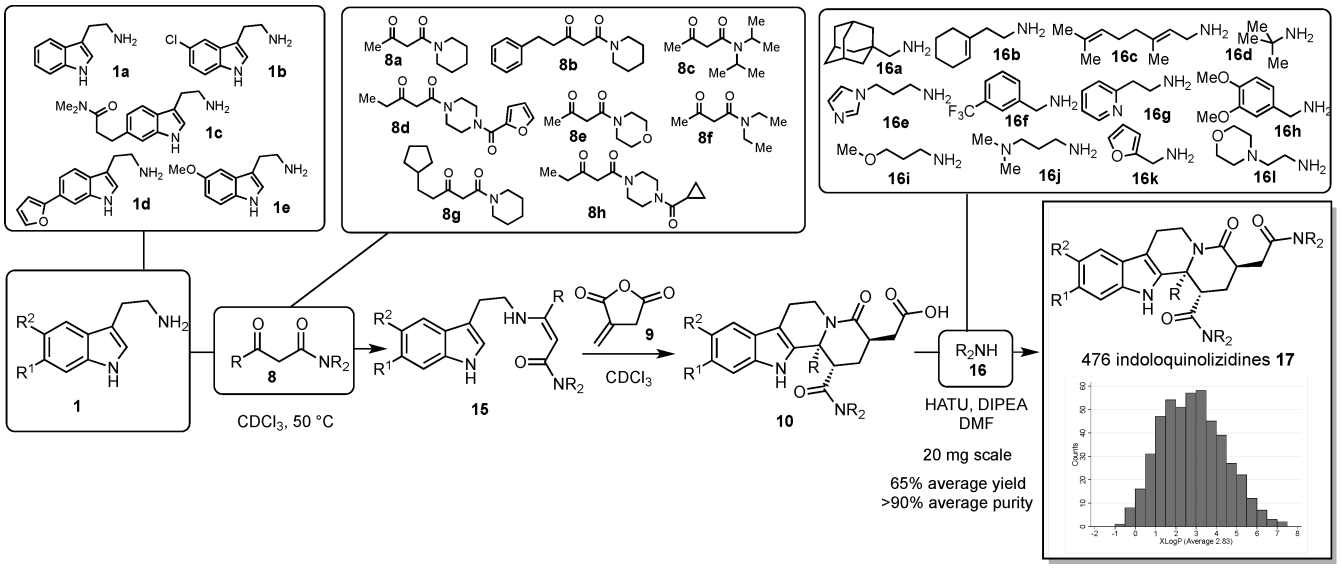
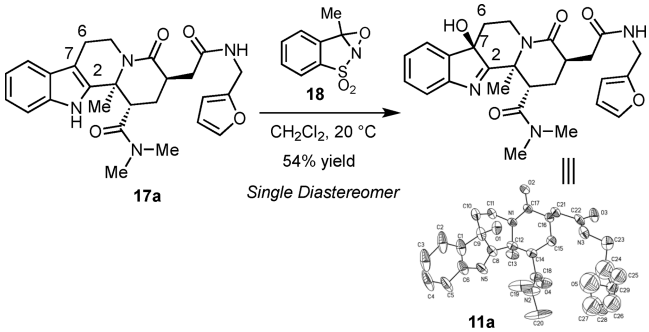


Figure 2. Synthesis of 476-member library of indoloquinolizidines. The assembly process entailed two chromatographic steps, including initial purification of each of the 40 acids **10** and subsequent LC−MS purification of all final library members **17**.

the initially produced acids **10** would be next diversified with 12 amines **16** to deliver the final library **17**. Selection of each of the building blocks shown in Figure 2 was guided by Accelrys Pipeline Pilot, which enabled virtual enumeration of the target library and estimation of various molecular properties in silico. Specifically, during the design process, we applied appropriate filters to select building blocks that would produce the target library with molecular weight below 600 and calculated logarithmic value of *n*-octanol/water partition coefficient (c log P) within a range of 1−5. The synthesis began with condensations of five tryptamines **1** with eight ketoamides **8**, followed by reactions of the resulting vinylogous ureas **15** with anhydride **9** to afford 40 indoloquinolizidine-containing carboxylic acids **10**. Each of the acids **10** was obtained as a single diastereomer approximately on a 500 mg scale in a single-flask operation starting with the corresponding tryptamines **1** and ketoamides **8**. To ensure their high chemical purity, all pyrrolidinone-containing carboxylic acids **10** were purified by conventional chromatography. The second stage of the synthesis entailed coupling of each of the acids **10** with 12 amines **16**. Following examination of several amide-coupling protocols, we established that this transformation can be efficiently accomplished using *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and *N*,*N*-diisopropylethylamine (DIPEA) in DMF. Preparative LC−MS purification of each final library member **17** established that 476 compounds were successfully produced on 20 mg scale in 65% average yield and >90% chemical purity.

Next, we examined a range of conditions that could promote chemoselective oxidation at the C(7) position of the indole moiety. This process emulates a putative conversion of strictosidine to hydroxy indolenine **4** (Figure 1A). We found that the use of oxaziridine **18**[11] efficiently promoted this conversion. A representative alcohol **11a** was obtained as a single diastereomer by treatment of the corresponding indoloquinolizidine **17a** with oxaziridine **18** at ambient temperature in dichloromethane (Scheme 3). The relative stereochemistry of **11a** was determined by X-ray crystallography.

Scheme 3. Synthesis of Hydroxyindoline 11a



We found that treatment of hydroxy indolenine **11b** with a dilute solution of a strong Brønsted acid triggered efficient conversion to a single reaction product. X-ray crystallography unambiguously established the structure of spirocyclic dihydroindolone **12a**,[12] which was produced with complete diastereoelectivity (Scheme 4). While this transformation was analogous to the putative biosynthetic conversion of hydroxy indolenine **4** into geissoschizine oxindole **5** (Figure 1A), the course of the rearrangement was altered, presumably because of the higher propensity of **11b** for protonation at the imine moiety, which induced subsequent [1,2]-shift with a concomitant cleavage of the C(6)−C(7) bond.

We next turned our attention to oxidative cleavage of indoloquinolizidine at the C(2)−C(7) bond. Biosynthetically, a similar transformation has been proposed to enable conversion of strictosidine **3** into pumiloside **7** via the intermediacy of **6** (Figure 1A). Among several oxidants examined, *m*-CPBA was found to be the most efficient reagent in promoting this oxidative cleavage. In a representative case, treatment of indoloquinolizidine **17b** with *m*-CPBA at ambient temperature furnished the desired ring-fragmented tricylic ketoamide **13a** in 71% yield (Scheme 5).

We also found that subjection of ketoamide **13b** to KOH in EtOH triggered efficient transannular aldol condensation with a concomitant dehydration.[13] This transformation produced tetracylic quinolone **14a**, which was isolated in 53% yield

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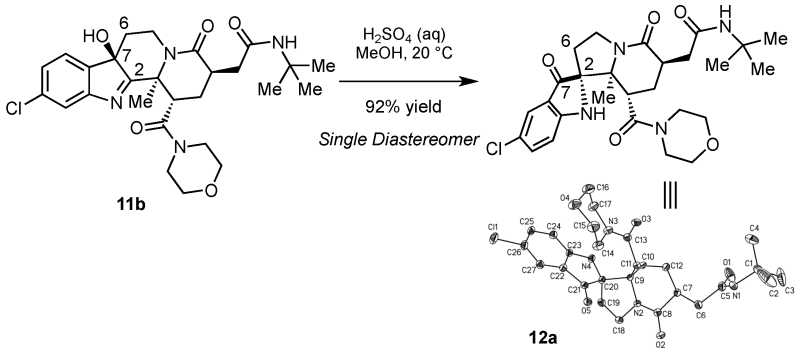
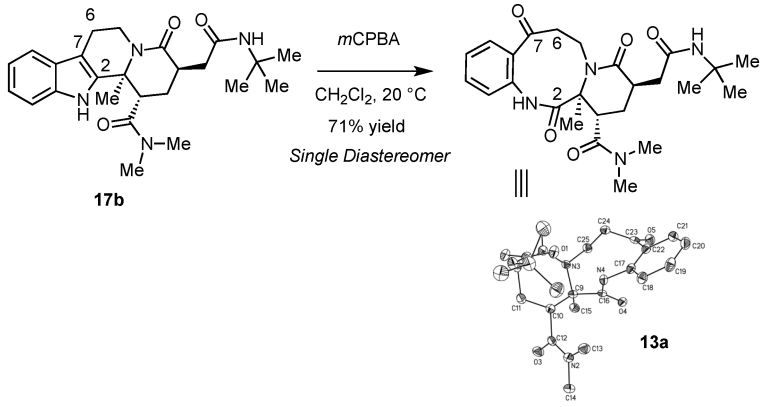
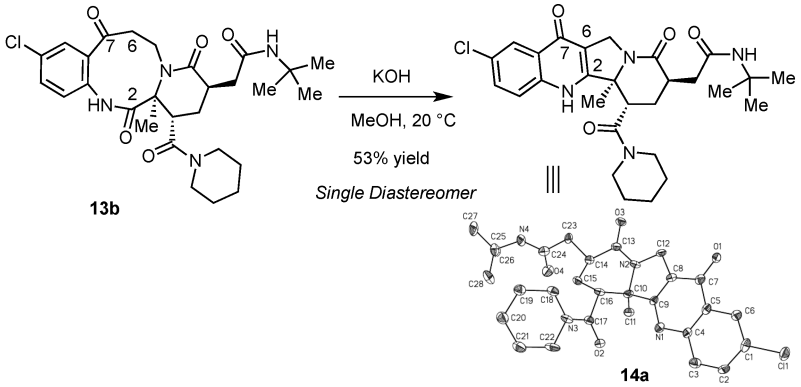
Scheme 4. Synthesis of Spirocyclic Dihydroindolone 12a



Scheme 5. Synthesis of Tricyclic Ketone 13a



Scheme 6. Synthesis of Pyrroloquinolone 14a



(Scheme 6). Combination of NMR spectroscopy with X-ray crystallography once again provided unambiguous structural assignments of this compound.

Having established an efficient skeletal diversification strategy, we aimed to apply this biogenesis-guided approach to parallel assembly of a new chemical library (Figure 3). The main challenge was to ensure that iterative processing and parallel diversification of each of the core structures within the library would be efficient and compatible with a range of synthetic precursors required for library synthesis. The parallel assembly process began with condensations of four readily available tryptamines **1** with each of the two ketoamides **8**, followed by treatment of the resulting vinylogous ureas with itaconic anhydride **9** to produce eight possible carboxylic acids **10** (75% average yield). The next stage of the assembly process entailed HATU-promoted coupling of 8 carboxylic acids **10** with 12 amines **16**, which successfully produced 96 possible amides **17** (74% average yield after parallel LC−MS purification). The first skeletal transformation entailed oxidation of indoloquinolizidines **17** with oxaziridine **18** to give the corresponding hydroxy indolenines, which displayed high propensity to undergo subsequent acid-catalyzed rearrangement and were used directly to produce the corresponding spirocyclic dihydroindolones **12**. We determined that 83 such reactions proceeded successfully to give final products **12** as single detectable diastereomers in high chemical purity (>90%) following LC−MS purification. The next skeletal transformation was accomplished by treatment of 96 indoloquinolizidines **17** with *m*-CPBA, which successfully produced 96 required ketoamides **13** (>90% purity by LC−MS). The final skeletal elaboration entailed base-promoted transannular aldol cyclization, followed by dehydration, which

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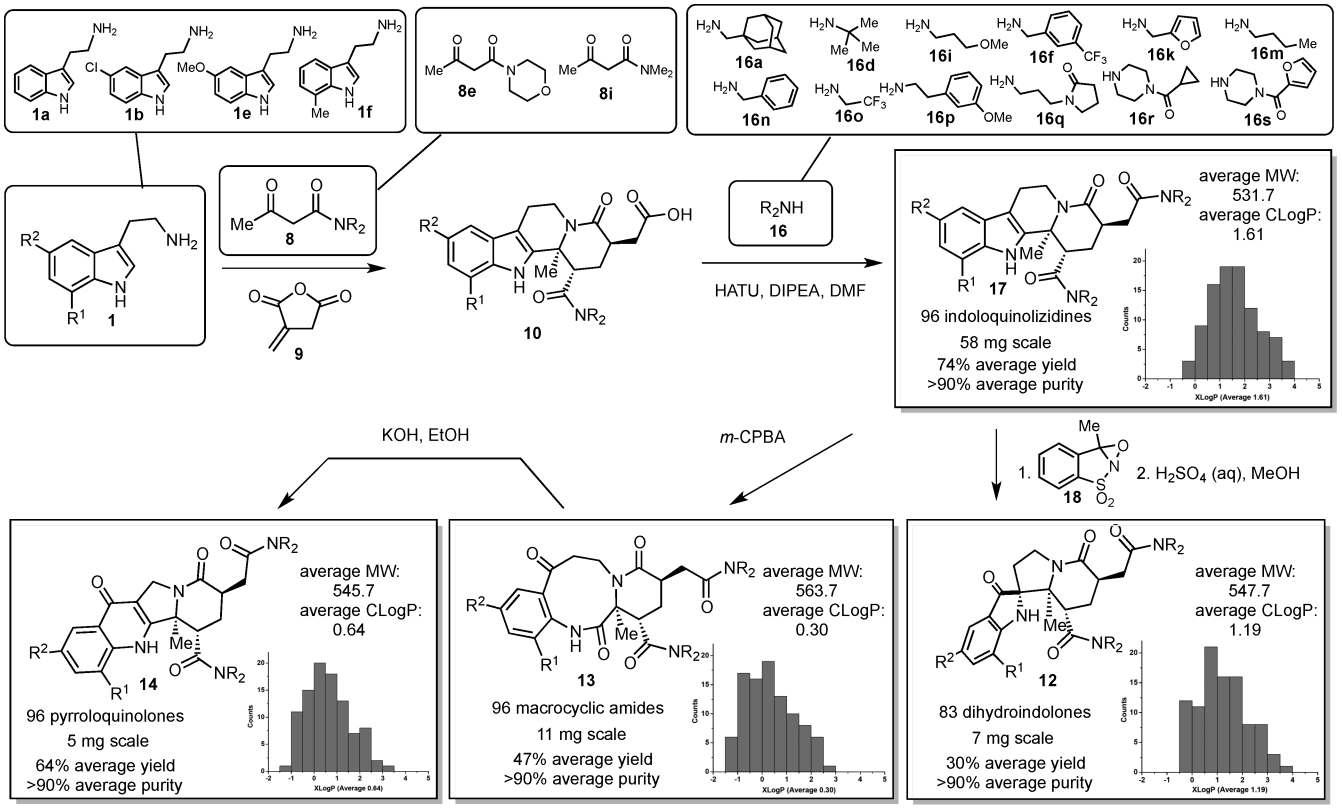

Figure 3. Synthesis of 371-member skeletally diverse small-molecule library. The assembly process mimics skeletal branching of monoterpenoid alkaloid biosynthesis and enables efficient conversion of the initially produced set of 96 indoloquinolizidines **17** into collections of skeletally distinct polycyclic products **12**, **13**, and **14**. The figure shows structures of building blocks used for library generation, depicts reaction conditions and scales, average yields, molecular weights, chemical purities as well as log P distributions.

was applied to all ketoamides **13** to give 96 tetracyclic quinolones **14** in 64% average yield (>90% purity by LC−MS). This operation completed the construction of 371-member chemical library. All final compounds were found to exhibit excellent chemical stability and highly favorable physicochemical properties (Figure 3). This effort validated the efficiency of our approach, as well as the compatibility of this biomimetic reaction sequence with a range of building blocks required for high-throughput organic synthesis.

Newly generated chemical libraries have been subjected to broad biological evaluation conducated at the NIH Molecular Libraries Probe Production Centers Network (MLPCN). Initial screening efforts resulted in identification of several compounds with promising activity in several assays including inhibition of fatty acid synthase thioesterase domain, antagonism of Smad3-specific TGF-β signaling pathway, and disruption of RIN1/ABL interaction.[14] In addition, our own screening effort recently identified a new chemical inducer of mitochondrial permeability transition.[15] These preliminary studies validate the general utility of this library for discovery of bioactive chemical probes and set the stage for subsequent pharmacological studies.

■ CONCLUSION

High-throughput synthesis of skeletally diverse small-molecule libraries remains challenging despite the notable progress achieved to date.[16] As natural products continue to stimulate innovation in chemical biology and drug discovery,[17] interest is growing in developing efficient approaches to chemical libraries that would approach the level of skeletal diversity found in nature. Inspired by the diversity-generating power of monoterpenoid alkaloid biosynthesis, we present an efficient synthetic strategy to a chemical library that mimics the skeletal diversity found in nature. After initial assembly of 476-member library of indoloquinolizidines, the core structure was transformed into three additional frameworks, generating a new library of 371 compounds that feature both skeletal and peripheral diversity. Preliminary high-throughout screening of this compound collection resulted in the identification of several useful chemical probes, setting the stage for their subsequent detailed pharmacological evaluation.

■ EXPERIMENTAL SECTION

General Experimental Methods. Common HPLC and ACS grade organic solvents were purchased and used without further purification. Dichloromethane and tetrahydrofuran were purified by distillation. Commercially available reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on ^{1}H 400, 500 MHz and ^{13}C 100, 125 MHz spectrometers using residual solvent peaks as an internal standard. High-resolution mass spectra were recorded with Q-TOF Ultima tandem quadrupole/Time-of-Flight instrument. LC−MS purification and analyses were performed using a LC−MS system consisting of a binary gradient module, a HPLC pump, a quadrupole mass spectrometer, a fluidics organizer, a sample manager, a dual channel UV−vis detector, and an evaporative light scattering detector. Fractions were collected by ES+ MS detection of product ion. Purity was determined by area under curve of either UV(214 nm) or ELS trace.

Indoloquinolizidine 10a. A solution of 5-chlorotryptamine **1b** (204.4 mg, 1.05 mmol) in $CHCl_3$ (3 mL) was treated with ketoamide **8a** (176.0 mg, 1.04 mmol) and 4 Å molecular sieves (0.25 g). The

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reaction mixture was heated at 50 °C overnight and filtered, and the filtrate was concentrated in vacuo. A solution of crude enamide in 1,4-dioxane (3 mL) was treated with itaconic anhydride **9** (122.2 mg, 1.04 mmol). The reaction mixture was heated at 40 °C overnight, followed by dropwise addition of HCl (4 M in 1,4-dioxane, 0.39 mL, 1.56 mmol). Stirring was continued for 3 h at the same temperature before the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (elution with $CHCl_2$:$CHCl_3$:MeOH = 2:2:1 + 2% formic acid) to give indoloquinolizidine **10a** (428.6 mg, 90%). White amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70−0.75 (m, 1H), 1.10−1.12 (m, 1H), 1.39−1.45 (m, 3H), 1.48−1.51 (m, 1H), 1.78 (d, 1H, J = 14.4 Hz), 1.91 (s, 3H), 2.58 (dt, 1H, J = 12.8, 12.0 Hz), 2.65−2.68 (m, 2H), 2.78−2.91 (m, 2H), 2.97−3.07 (m, 4H), 3.31−3.41 (m, 2H), 3.58−3.66 (m, 1H), 5.04 (dd, 1H, J = 12.4, 1.6 Hz), 7.03 (d, 1H, J = 8.8 Hz), 7.24 (d, 1H, J = 8.0 Hz), 7.43 (s, 1H), 9.08 (s, 1H), 11.3 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 23.9, 25.3, 25.9, 27.3, 34.6, 37.5, 37.7, 43.6, 45.9, 47.2, 59.7, 108.7, 112.0, 117.7, 122.3, 125.0, 126.9, 134.2, 137.3, 170.6, 171.7, 175.8; HRMS (ESI) calculated for $C_{24}H_{29}N_3O_4Cl$ 458.1847 $[M + H]^+$, found 458.1838. Single crystals for X-ray analysis were obtained by slow evaporation of saturated solution method. CCDC number is 791451.

Indoloquinolizidine 10b. A solution of 5-chlorotryptamine **1b** (205.5 mg, 1.06 mmol) in $CHCl_3$ (4 mL) was treated with ketoamide **8b** (273.1 mg, 1.05 mmol) and 4 Å molecular sieves (0.25 g). The reaction mixture was heated at 50 °C overnight and filtered, and the filtrate was concentrated in vacuo. A solution of crude enamide in 1,4-dioxane (4 mL) was treated with itaconic anhydride **9** (114.7 mg, 1.02 mmol). The reaction mixture was heated at 40 °C overnight, followed by dropwise addition of HCl (4 M in 1,4-dioxane, 0.40 mL, 1.60 mmol). Stirring was continued for 3 h at the same temperature before the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (elution with $CHCl_2$:$CHCl_3$:MeOH = 2:2:1 + 2% formic acid) to give indoloquinolizidine **10b** (322.9 mg, 56%). White amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.28 (br s, 1H), 0.92 (br s, 1H), 1.16 (s, 1H), 1.37 (s, 1H), 1.68 (dd, 1H, J = 7.5, 5.5 Hz), 2.30 (t, 1H, J = 11.3 Hz), 2.41 (td, 1H, J = 14.0, 4.4 Hz), 2.52 (td, 1H, J = 12.6, 4.1 Hz), 2.61−2.89 (m, 7H), 2.93−3.18 (m, 6H), 3.40 (dd, 1H, J = 11.2, 7.9 Hz), 3.51−3.60 (m, 1H), 5.26 (d, 1H, J = 8.6), 7.06 (dd, 3H, J = 11.5, 4.5 Hz), 7.10 (t, 1H, J = 7.3 Hz), 7.18 (t, 2H, J = 7.5 Hz), 7.30 (d, 1H, J = 8.6 Hz), 7.45 (s, 1H), 9.67 (s, 1H), 11.45 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 23.9, 25.4, 25.9, 27.5, 31.3, 34.6, 37.0, 37.5, 40.9, 43.9, 47.4, 48.2, 62.7, 110.8, 112.4, 117.9, 122.7, 125.3, 126.1, 127.1, 128.3, 128.5, 134.7, 134.9, 141.2, 171.3, 171.6, 176.8; HRMS (ESI) calculated for $C_{31}H_{35}N_3O_4Cl$ 548.2316 $[M + H]^+$, found 548.2319. Single crystals for X-ray analysis were obtained by slow evaporation of saturated solution method. CCDC number is 900900.

Indoloquinolizidine 10c. A solution of tryptamine **1a** (170.9 mg, 1.05 mmol) in $CHCl_3$ (3 mL) was treated with 1-morpholinobutane-1,3-dione **8e** (181.3 mg, 1.04 mmol) and 4 Å molecular sieves (0.25 g). The reaction mixture was heated at 50 °C overnight and filtered, and the filtrate was concentrated in vacuo. To a solution of crude enamide in 1,4-dioxane (3 mL) was added itaconic anhydride **9** (122.2 mg, 1.04 mmol). The reaction mixture was heated at 40 °C overnight, followed by dropwise addition of HCl (4 M in 1,4-dioxane, 0.39 mL, 1.56 mmol). Stirring was continued for 3 h at the same temperature before the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (elution with EtOAc:$CHCl_3$:MeOH = 5:5:1 + 2% formic acid) to give indoloquinolizidine **10c** (429.2 mg, 97%). White amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77 (dt, 1H, J = 13.5, 3.5 Hz), 1.90 (s, 3H), 2.61 (dt, 1H, J = 13.5, 11.5 Hz), 2.73−2.82 (m, 4H), 2.87−2.94 (m, 2H), 2.99−3.03 (m, 1H), 3.04−3.09 (m, 2H), 3.12−3.16 (m, 1H), 3.37 (dd, 1H, J = 13.0, 5.0 Hz), 3.49 (d, 2H, J = 8.0 Hz), 3.58 (t, 1H, J = 7.5 Hz), 3.61−3.66 (m, 1H), 5.05 (d, 1H, J = 11.5 Hz), 7.03−7.07 (m, 2H), 7.27 (d, 1H, J = 7.5 Hz), 7.47 (d, 1H, J = 8.0 Hz), 8.87 (s, 1H), 10.65 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 21.2, 27.3, 34.5, 37.6, 37.7, 42.5, 45.9, 46.2, 59.6, 65.8, 66.3, 109.3, 111.0, 118.3, 119.6, 122.3, 125.9, 135.5, 135.8, 170.6, 172.3, 175.6; HRMS (ESI) calculated for $C_{23}H_{28}N_3O_5$ 426.2029 $[M + H]^+$, found 426.2016.

Indoloquinolizidine 10d. It was prepared from tryptamine **1a**, ketoamide **8a**, and itaconic anhydride **9** in 339.6 mg, 80% yield by following the same protocol of **10c**. White amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82−0.85 (m, 1H), 1.16−1.18 (m, 1H), 1.34−1.38 (m, 1H), 1.43−1.45 (m, 2H), 1.47−1.51 (m, 1H), 1.78 (dt, 1H, J = 14.0, 4.0 Hz), 1.94 (s, 3H), 2.59 (dt, 1H, J = 13.5, 11.0 Hz), 2.72−2.76 (m, 1H), 2.77−2.78 (m, 1H), 2.83 (dd, 1H, J = 17.0, 5.0 Hz), 2.89−2.97 (m, 2H), 3.01−3.06 (m, 1H), 3.07−3.18 (m, 2H), 3.31 (dd, 1H, J = 13.5, 5.0 Hz), 3.43−3.46 (m, 1H), 3.59−3.63 (m, 1H), 5.05 (dd, 1H, J = 12.5, 2.5 Hz), 7.07 (t, 1H, J = 7.5 Hz), 7.13 (t, 1H, J = 7.5 Hz), 7.29 (d, 1H, J = 8.5 Hz), 7.47 (d, 1H, J = 8.0 Hz), 8.85 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.4, 24.1, 25.5, 26.2, 27.5, 34.9, 37.8, 38.2, 43.5, 46.0, 47.3, 60.0, 109.0, 111.1, 118.3, 119.5, 122.2, 126.0, 135.9, 136.0, 171.0, 171.8, 175.6; HRMS (ESI) calculated for $C_{24}H_{30}N_3O_4$ 424.2236 $[M + H]^+$, found 424.2223.

Indoloquinolizidine 10e. It was prepared from tryptamine **1a**, ketoamide **8g**, and itaconic anhydride **9** in 320.4 mg, 63% yield by following the same protocol of **10c**. Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84−0.88 (m, 1H), 0.90−0.99 (m, 2H), 1.31−1.36 (m, 1H), 1.42−1.50 (m, 4H), 1.62−1.67 (m, 1H), 1.68−1.74 (m, 3H), 2.14−2.20 (m, 1H), 2.21−2.26 (m, 1H), 2.58−2.60 (m, 1H), 2.70−2.74 (m, 4H), 2.75−2.80 (m, 1H), 2.82−2.86 (m, 1H), 2.89−2.95 (m, 2H), 3.01−3.06 (m, 1H), 3.10 (dd, 1H, J = 17.0, 5.0 Hz), 3.29−3.35 (m, 3H), 3.48−3.51 (m, 1H), 3.60−3.63 (m, 1H), 5.22 (dd, 1H, J = 12.0, 2.5 Hz), 7.04−7.10 (m, 2H), 7.28 (d, 1H, J = 7.0 Hz), 7.50 (d, 1H, J = 7.0 Hz), 8.95 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 25.1, 25.1, 27.4, 31.1, 32.5, 32.8, 33.6, 34.2, 37.1, 40.3, 40.7, 42.5, 46.1, 47.9, 62.5, 65.5, 66.1, 110.9, 110.9, 118.3, 119.7, 122.3, 126.0, 133.6, 136.0, 171.2, 171.9, 176.0; HRMS (ESI) calculated for $C_{29}H_{38}N_3O_5$ 508.2811 $[M + H]^+$, found 508.2798.

Indoloquinolizidine 10f. It was prepared from tryptamine **1a**, ketoamide **8i**, and itaconic anhydride **9** in 211.5 mg, 55% yield by following the same protocol of **10c**. White amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (dt, 1H, J = 13.0, 3.5 Hz), 1.90 (s, 3H), 2.58 (s, 3H), 2.72−2.86 (m, 3H), 2.87−2.93 (m, 4H), 2.97−3.05 (m, 3H), 3.36 (dd, 1H, J = 13.0, 4.5 Hz), 5.06 (d, 1H, J = 11.0 Hz), 7.06 (t, 1H, J = 7.5 Hz), 7.11 (t, 1H, J = 7.5 Hz), 7.32 (d, 1H, J = 8.0 Hz), 7.47 (t, 1H, J = 7.5 Hz), 9.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 21.0, 26.6, 34.6, 36.1, 37.2, 37.6, 37.7, 46.0, 59.5, 109.0, 111.1, 118.0, 119.2, 121.9, 125.7, 135.6, 135.9, 170.6, 173.5, 175.3; HRMS (ESI) calculated for $C_{21}H_{26}N_3O_4$ 384.1923 $[M + H]^+$, found 384.1923.

Indoloquinolizidine 10g. It was prepared from tryptamine **1b**, ketoamide **8i**, and itaconic anhydride **9** in 263.7 mg, 63% yield by following the same protocol of **10c**. Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79 (dt, 1H, J = 13.0, 3.5 Hz), 1.88 (s, 3H), 2.52−2.57 (m, 1H), 2.60 (s, 3H), 2.64−2.79 (m, 3H), 2.80−2.85 (m, 1H), 2.89 (s, 3H), 2.97−3.01 (m, 2H), 3.32 (dd, 1H, J = 13.0, 5.0 Hz), 5.03 (d, 1H, J = 11.0 Hz), 7.02 (d, 1H, J = 9.0 Hz), 7.21 (d, 1H, J = 8.5 Hz), 7.42 (s, 1H), 9.07 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 26.9, 34.7, 36.3, 37.4, 37.6, 37.9, 46.3, 59.6, 108.9, 112.2, 117.8, 122.3, 125.2, 126.9, 134.3, 137.3, 170.7, 173.6, 175.9; HRMS (ESI) calculated for $C_{21}H_{25}N_3O_4Cl$ 418.1534 $[M + H]^+$, found 418.1534.

Indoloquinolizidine 10h. It was prepared from tryptamine **1b**, ketoamide **8e**, and itaconic anhydride **9** in 299.3 mg, 65% yield by following the same protocol of **10c**. Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 (dt, 1H, J = 13.5, 3.5 Hz), 1.91 (s, 3H), 2.58 (dt, 1H, J = 13.5, 11.0 Hz), 2.70−2.75 (m, 3H), 2.85−2.90 (m, 2H), 2.98−3.07 (m, 3H), 3.17−3.22 (m, 2H), 3.33 (dd, 1H, J = 13.0, 5.0 Hz), 3.47−3.53 (m, 2H), 3.58−3.64 (m, 2H), 5.04 (d, 1H, J = 11.5 Hz), 7.02 (dd, 1H, J = 8.5, 2.0 Hz), 7.18 (d, 1H, J = 9.0 Hz), 7.44 (d, 1H, J = 1.5 Hz), 8.92 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 27.4, 34.6, 37.7, 42.6, 46.0, 46.3, 59.7, 66.1, 66.4, 109.2, 112.0, 118.0, 122.7, 125.4, 127.0, 134.2, 137.1, 170.6, 172.3, 175.8; HRMS (ESI) calculated for $C_{23}H_{27}N_3O_5Cl$ 460.1639 $[M + H]^+$, found 460.1639.

Indoloquinolizidine 10i. It was prepared from tryptamine **1c**, ketoamide **8f**, and itaconic anhydride **9** in 250.6 mg, 49% yield by following the same protocol of **10c**. Pale yellow amorphous solid: ^{1}H

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NMR (500 MHz, $CDCl_3$) δ 0.64 (t, 3H, J = 7.0 Hz), 1.11 (t, 3H, J = 7.0 Hz), 1.75−1.77 (m, 1H), 1.90 (s, 3H), 2.57−2.65 (m, 3H), 2.69−2.75 (m, 2H), 2.77−2.86 (m, 3H), 2.89−2.96 (m, 8H), 3.01−3.07 (m, 4H), 3.22 (dd, 1H, J = 13.5, 4.5 Hz), 3.26 (dd, 1H, J = 13.5, 7.0 Hz), 3.38−3.43 (m, 1H), 5.03 (d, 1H, J = 12.5 Hz), 6.95 (d, 1H, J = 8.0 Hz), 7.09 (s, 1H), 7.37 (d, 1H, J = 8.0 Hz), 8.42 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9, 14.2, 21.1, 21.2, 27.6, 31.7, 34.9, 35.5, 36.0, 37.2, 37.5, 38.2, 41.2, 42.6, 46.5, 59.5, 108.8, 110.5, 118.3, 120.3, 124.4, 135.6, 135.7, 136.1, 170.8, 172.6, 173.0, 175.5; HRMS (ESI) calculated for $C_{28}H_{39}N_4O_5$ 511.2920 $[M + H]^+$, found 511.2913.

Indoloquinolizidine 10j. It was prepared from tryptamine **1e**, ketoamide **8a**, and itaconic anhydride **9** in 390.9 mg, 86% yield by following the same protocol of **10c**. Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88−0.92 (m, 1H), 1.19−1.24 (m, 1H), 1.43−1.50 (m, 4H), 1.76 (dt, 1H, J = 13.0, 4.0 Hz), 1.95 (s, 3H), 2.55−2.62 (m, 1H), 2.76−2.78 (m, 2H), 2.82−2.95 (m, 3H), 3.02−3.05 (m, 1H), 3.14−3.17 (m, 2H), 3.27 (dd, 1H, J = 13.5, 5.0 Hz), 3.42−3.49 (m, 1H), 3.63−3.66 (m, 1H), 3.83 (s, 3H), 5.05 (dt, 1H, J = 12.0, 2.0 Hz), 6.80 (dd, 1H, J = 9.0, 2.5 Hz), 6.92 (d, 1H, J = 2.5 Hz), 7.18 (d, 1H, J = 8.5 Hz), 8.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.5, 24.2, 25.6, 26.3, 27.7, 35.0, 37.8, 38.5, 43.5, 46.0, 47.3, 55.9, 60.1, 100.3, 108.7, 111.8, 112.3, 126.3, 130.9, 136.7, 154.1, 171.1, 171.7, 175.0; HRMS (ESI) calculated for $C_{25}H_{32}N_3O_5$ 454.2342 $[M + H]^+$, found 454.2334.

Indoloquinolizidine 10k. It was prepared from tryptamine **1e**, ketoamide **8b**, and itaconic anhydride **9** in 381.2 mg, 70% yield by following the same protocol of **10c**. Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.39−0.42 (m, 1H), 0.92−0.94 (m, 1H), 1.21−1.28 (m, 3H), 1.39−1.42 (m, 1H), 1.73−1.75 (m, 1H), 2.37−2.43 (m, 2H), 2.53−2.58 (m, 1H), 2.62−2.65 (m, 1H), 2.76−2.80 (m, 2H), 2.88−2.92 (m, 3H), 3.03−3.07 (m, 3H), 3.18−3.23 (m, 2H), 3.37 (dd, 1H, J = 12.5, 6.0 Hz), 3.62−3.64 (m, 1H), 3.84 (s, 3H), 5.29 (d, 1H, J = 8.5 Hz), 6.80 (d, 1H, J = 9.0 Hz), 6.96 (s, 1H), 7.07−7.14 (m, 3H), 7.19−7.26 (m, 3H), 8.94 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 23.9, 25.3, 25.7, 27.5, 31.3, 34.6, 37.0, 37.4, 40.9, 43.6, 47.2, 48.1, 55.9, 62.6, 100.3, 110.7, 111.9, 112.3, 126.0, 126.4, 128.2, 128.4, 131.3, 134.1, 141.3, 154.0, 171.4, 171.5, 176.2; HRMS (ESI) calculated for $C_{32}H_{38}N_3O_5$ 544.2811 $[M + H]^+$, found 544.2794.

Indoloquinolizidine 10l. It was prepared from tryptamine **1e**, ketoamide **8i**, and itaconic anhydride **9** in 285.8 mg, 69% yield by following the same protocol of **10c**. Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79 (dt, 1H, J = 13.0, 3.5 Hz), 1.93 (s, 3H), 2.52−2.59 (m, 1H), 2.72 (s, 3H), 2.74−2.76 (m, 2H), 2.82−2.85 (m, 1H), 2.86−2.91 (m, 2H), 2.92 (s, 3H), 3.01−3.06 (m, 1H), 3.27 (dd, 1H, J = 13.5, 5.0 Hz), 3.83 (s, 3H), 5.06 (d, 1H, J = 11.0 Hz), 6.81 (dd, 1H, J = 8.5, 2.5 Hz), 6.92 (d, 1H, J = 2.5 Hz), 7.19 (d, 1H, J = 8.5 Hz), 8.62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 26.9, 34.9, 36.2, 37.5, 37.7, 38.2, 46.2, 55.9, 59.8, 100.3, 108.8, 112.0, 112.1, 126.2, 131.0, 136.6, 154.0, 170.9, 173.6, 175.8; HRMS (ESI) calculated for $C_{22}H_{28}N_3O_5$ 414.2029 $[M + H]^+$, found 414.2037.

Indoloquinolizidine 10m. It was prepared from tryptamine **1e**, ketoamide **8e**, and itaconic anhydride **9** in 429.1 mg, 94% yield by following the same protocol of **10c**. Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75 (dt, 1H, J = 13.0, 4.0 Hz), 1.89 (s, 3H), 2.58 (dt, 1H, J = 13.5, 11.0 Hz), 2.71−2.82 (m, 4H), 2.87−2.91 (m, 1H), 2.98−3.07 (m, 3H), 3.12−3.19 (m, 2H), 3.35 (dd, 1H, J = 13.0, 5.0 Hz), 3.48−3.52 (m, 2H), 3.58−3.65 (m, 2H), 3.76 (s, 3H), 5.04 (d, 1H, J = 12.0 Hz), 6.71 (dd, 1H, J = 8.5, 2.0 Hz), 6.92 (d, 1H, J = 2.0 Hz), 7.15 (d, 1H, J = 8.5 Hz), 8.69 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.3, 27.4, 34.6, 37.7, 37.8, 42.5, 46.0, 46.3, 55.8, 59.7, 66.0, 66.4, 100.6, 109.1, 111.7, 112.2, 126.3, 131.0, 136.4, 154.1, 170.7, 172.3, 175.7; HRMS (ESI) calculated for $C_{24}H_{30}N_3O_6$ 456.2135 $[M + H]^+$, found 456.2134.

Indoloquinolizidine 10n. It was prepared from tryptamine **1f**, ketoamide **8i**, and itaconic anhydride **9** in 310.6 mg, 78% yield by following the same protocol of **10c**. Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79 (dt, 1H, J = 13.0, 3.5 Hz), 1.99 (s, 3H), 2.43 (s, 3H), 2.59 (dt, 1H, J = 13.5, 10.5 Hz), 2.77 (s, 3H), 2.79−2.81 (m, 2H), 2.86−2.89 (m, 2H), 2.95 (s, 3H), 2.96−3.00 (m, 1H), 3.06−3.09 (m, 1H), 3.24 (dd, 1H, J = 13.5, 5.0 Hz), 5.05 (dd, 1H, J = 13.0, 3.0 Hz), 6.98 (d, 1H, J = 7.5 Hz), 7.04 (t, 1H, J = 7.5 Hz), 7.35 (d, 1H, J = 7.5 Hz), 8.55 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5, 21.1, 26.6, 34.8, 35.5, 36.0, 37.3, 37.6, 37.9, 46.0, 59.7, 109.6, 115.9, 119.6, 120.3, 122.6, 125.4, 135.2, 135.6, 170.7, 173.6, 175.5; HRMS (ESI) calculated for $C_{22}H_{28}N_3O_4$ 398.2080 $[M + H]^+$, found 398.2081.

Indoloquinolizidine 10o. It was prepared from tryptamine **1f**, ketoamide **8e**, and itaconic anhydride **9** in 339.2 mg, 77% yield by following the same protocol of **10c**. Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 (dt, 1H, J = 13.0, 4.0 Hz), 1.98 (s, 3H), 2.42 (s, 3H), 2.60 (dt, 1H, J = 13.5, 10.5 Hz), 2.75−2.80 (m, 3H), 2.93−3.03 (m, 3H), 3.09−3.14 (m, 1H), 3.25−3.31 (m, 2H), 3.33−3.38 (m, 1H), 3.39−3.43 (m, 1H), 3.49−3.52 (m, 1H), 3.58−3.61 (m, 2H), 3.75 (dt, 1H, J = 13.0, 5.0 Hz), 5.03 (dd, 1H, J = 12.0, 3.0 Hz), 6.98 (d, 1H, J = 7.0 Hz), 7.04 (t, 1H, J = 7.0 Hz), 7.34 (d, 1H, J = 7.5 Hz), 8.48 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 21.2, 21.4, 27.5, 34.8, 37.8, 38.1, 42.2, 46.0, 46.2, 59.8, 66.4, 66.5, 109.7, 116.0, 119.9, 120.1, 122.9, 125.4, 135.2, 135.3, 170.8, 172.4, 174.9; HRMS (ESI) calculated for $C_{24}H_{30}N_3O_5$ 440.2185 $[M + H]^+$, found 440.2183.

Indoloquinolizidine 17a. A solution of indoloquinolizidine **10f** (15.3 mg, 0.040 mmol) and amine **16k** (3 equiv.) in 1:1 THF−$CHCl_3$ (1.0 mL) was treated with EDCI (13.0 mg, 0.066 mmol), HOBt (8.1 mg, 0.060 mmol) and DIPEA (25 μL, 0.14 mmol). The reaction mixture was stirred overnight at room temperature, and then solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (elution with EtOAc:MeOH = 20:1) to give indoloquinolizidine **17a** (12.6 mg, 68%). Pale yellow liquid: ^{1}H NMR (500 MHz, CD_3OD) δ 1.68 (dt, 1H, J = 14.0, 4.0 Hz), 1.85 (s, 3H), 2.47−2.54 (m, 1H), 2.55 (s, 3H), 2.69 (d, 2H, J = 6.0 Hz), 2.75−2.77 (m, 2H), 2.95 (s, 3H), 2.97−3.01 (m, 1H), 3.05−3.08 (m, 1H), 3.50 (dd, 1H, J = 12.0, 4.5 Hz), 4.28 (d, 1H, J = 15.5 Hz), 4.34 (d, 1H, J = 15.5 Hz), 4.97 (dt, 1H, J = 10.0, 2.5 Hz), 6.21−6.22 (m, 1H), 6.30−6.31 (m, 1H), 7.01 (t, 1H, J = 8.0 Hz), 7.10 (t, 1H, J = 7.5 Hz), 7.32 (d, 1H, J = 8.0 Hz), 7.35−7.36 (m, 1H), 7.43 (d, 1H, J = 7.5 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 22.0, 22.3, 27.5, 36.4, 36.7, 37.1, 37.7, 39.2, 40.1, 46.0, 61.5, 108.1, 110.4, 111.3, 112.3, 119.0, 120.3, 123.0, 127.6, 137.5, 138.0, 143.3, 153.1, 173.4, 173.7, 174.4; HRMS (ESI) calculated for $C_{26}H_{31}N_4O_4$ 463.2345 $[M + H]^+$, found 463.2349.

Indoloquinolizidine 17c. It was prepared from indoloquinolizidine **10b** and amine **16j** in 17.9 mg, 71% yield by following the same protocol of **17a**. Pale yellow liquid: ^{1}H NMR (500 MHz, CDCl3) δ 0.78−0.88 (m, 1H), 1.34 (ddd, 3H J = 15.8, 11.8, 11.3 Hz), 1.44−1.54 (m, 2H), 1.71−1.82 (m, 2H), 1.89−1.97 (m, 1H), 2.40 (s, 7H), 2.44−2.67 (m, 6H), 2.78 (dd, 1H, J = 11.6, 4.8 Hz), 2.85−2.96 (m, 2H), 3.02−3.13 (m, 2H), 3.25 (t, 2H, J = 5.4 Hz), 3.32−3.47 (m, 5H), 3.63 (s, 1H), 5.30 (dd, 1H, J = 13.1, 3.9 Hz), 7.13−7.21 (m, 5H), 7.28 (s, 1H), 7.29 (d, 1H, J = 2.9 Hz), 7.32 (d, 1H, J = 2.3 Hz), 7.54 (d, 1H, J = 1.8 Hz), 8.92 (s, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 20.8, 24.3, 25.6, 26.0, 26.6, 27.3, 31.5, 35.4, 37.6, 38.3, 39.4, 40.3, 43.3, 45.0, 47.4, 48.2, 57.7, 62.4, 110.7, 112.2, 117.9, 122.4, 125.2, 126.0, 127.3, 128.3, 128.4, 134.4, 135.7, 141.4, 171.4, 171.6, 171.9; HRMS (ESI) calculated for $C_{36}H_{47}N_5O_3Cl$ 632.3367 $[M + H]^+$, found 632.3364.

Indoloquinolizidine 17d. It was prepared from indoloquinolizidine **10d** and amine **16c** in 17.2 mg, 77% yield by following the same protocol of **17a**. Pale yellow liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02−1.06 (m, 1H), 1.36−1.42 (m, 1H), 1.44−1.49 (m, 2H), 1.52−1.56 (m, 2H), 1.57 (s, 3H), 1.62 (s, 3H), 1.67 (s, 3H), 1.92−1.95 (m, 2H), 1.98 (s, 3H), 2.01−2.07 (m, 3H), 2.47−2.52 (m, 2H), 2.73−2.79 (m, 2H), 2.90−2.97 (m, 3H), 3.22 (dd, 1H, J = 13.5, 5.0 Hz), 3.29−3.33 (m, 2H), 3.51−3.55 (m, 1H), 3.61−3.65 (m, 1H), 3.73−3.82 (m, 2H), 5.02−5.04 (m, 1H), 5.06−5.11 (m, 2H), 5.91 (t, 1H, J = 4.5 Hz), 7.09 (t, 1H, J = 7.5 Hz), 7.16 (t, 1H, J = 7.5 Hz), 7.28 (d, 1H, J = 7.5 Hz), 7.48 (t, 1H, J = 8.0 Hz), 8.73 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.2, 17.6, 21.3, 21.8, 24.3, 25.7, 25.7, 26.4, 26.6, 26.7, 36.4, 37.4, 37.4, 39.5, 40.1, 43.3, 46.1, 47.3, 59.9, 108.8, 111.0, 118.3, 119.4, 119.9, 122.0, 123.8, 126.1, 131.7, 135.7, 136.6, 139.8, 170.7, 171.0, 172.2; HRMS (ESI) calculated for $C_{34}H_{47}N_4O_3$ 559.3648 $[M + H]^+$, found 559.3633.

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Indoloquinolizidine 17e. It was prepared from indoloquinolizidine **10d** and amine **16f** in 14.0 mg, 60% yield by following the same protocol of **17a**. Pale yellow liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94−1.00 (m, 1H), 1.26−1.32 (m, 1H), 1.41−1.47 (m, 2H), 1.49−1.54 (m, 2H), 1.98 (s, 3H), 2.05 (ddd, 1H, J = 14.0, 5.0, 3.0 Hz), 2.49 (dt, 1H, J = 14.0, 11.0 Hz), 2.55−2.59 (m, 1H), 2.64−2.70 (m, 1H), 2.78−2.82 (m, 1H), 2.92 (dd, 1H, J = 12.0, 3.5 Hz), 2.95−3.02 (m, 2H), 3.15−3.22 (m, 3H), 3.55−3.61 (m, 2H), 4.40−4.49 (m, 2H), 5.05 (ddd, 1H, J = 12.5, 4.5, 1.0 Hz), 6.72 (m, 1H), 7.09 (t, 1H, J = 7.0 Hz), 7.17 (dt, 1H, J = 7.5, 1.0 Hz), 7.29 (d, 1H, J = 8.0 Hz), 7.33 (d, 1H, J = 8.0 Hz), 7.42 (d, 1H, J = 7.5 Hz), 7.46−7.52 (m, 3H), 8.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.6, 24.3, 25.7, 26.5, 27.0, 36.2, 37.4, 39.9, 42.9, 43.3, 46.2, 47.1, 60.0, 108.8, 111.1, 118.3, 119.4, 122.1, 124.0 (J_{CF} = 273 Hz), 124.2 (J_{CF} = 3.9 Hz), 124.3 (J_{CF} = 3.6 Hz), 126.0, 129.0, 130.6 (J_{CF} = 1.4 Hz), 130.9 (J_{CF} = 32.3 Hz), 135.7, 136.4, 139.6, 170.8, 171.6, 172.0; HRMS (ESI) calculated for $C_{32}H_{36}N_4O_3F_3$ 581.2740 $[M + H]^+$, found 581.2727.

Indoloquinolizidine 17f. It was prepared from indoloquinolizidine **10d** and amine **16i** in 17.6 mg, 89% yield by following the same protocol of **17a**. Pale yellow liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05−1.09 (m, 1H), 1.37−1.39 (m, 1H), 1.44−1.48 (m, 2H), 1.50−1.56 (m, 2H), 1.70−1.75 (m, 2H), 1.97 (s, 3H), 2.02 (ddd, 1H, J = 14.0, 4.5, 3.0 Hz), 2.47 (dt, 1H, J = 14.0, 10.5 Hz), 2.54 (dd, 1H, J = 14.5, 4.5 Hz), 2.74−2.80 (m, 2H), 2.86 (dd, 1H, J = 14.5, 6.0 Hz), 2.93−2.96 (m, 2H), 3.24−3.34 (m, 8H), 3.42 (t, 2H, J = 6.0 Hz), 3.55−3.60 (m, 2H), 5.07 (ddd, 1H, J = 11.5, 3.0, 1.5 Hz), 6.35 (t, 1H, J = 5.0 Hz), 7.10 (t, 1H, J = 7.5 Hz), 7.16 (t, 1H, J = 7.5 Hz), 7.29 (d, 1H, J = 8.0 Hz), 7.48 (d, 1H, J = 8.0 Hz), 8.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.8, 24.3, 25.7, 26.5, 26.8, 29.2, 36.3, 37.3, 37.7, 40.0, 43.3, 46.0, 47.3, 58.7, 59.9, 71.3, 108.8, 111.0, 118.3, 119.3, 122.0, 126.1, 135.7, 136.6, 170.8, 171.2, 172.2; HRMS (ESI) calculated for $C_{28}H_{39}N_4O_4$ 495.2971 $[M + H]^+$, found 495.2973.

Indoloquinolizidine 17g. It was prepared from indoloquinolizidine **10d** and amine **16k** in 12.5 mg, 62% yield by following the same protocol of **17a**. Pale yellow liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99−1.04 (m, 1H), 1.33−1.37 (m, 1H), 1.42−1.47 (m, 2H), 1.50−1.56 (m, 2H), 1.98 (s, 3H), 2.08 (ddd, 1H, J = 14.5, 5.0, 3.5 Hz), 2.43−2.50 (m, 2H), 2.55−2.61 (m, 1H), 2.75 (ddd, 1H, J = 14.0, 2.0, 1.0 Hz), 2.90 (dd, 1H, J = 12.5, 3.0 Hz), 2.97−3.00 (m, 1H), 3.08 (dd, 1H, J = 14.0, 5.0 Hz), 3.17 (dd, 1H, J = 14.0, 5.0 Hz), 3.23−3.25 (m, 2H), 3.47−3.52 (m, 1H), 3.61−3.66 (m, 1H), 4.18 (dd, 1H, J = 15.5, 4.5 Hz), 4.55 (dd, 1H, J = 15.5, 6.5 Hz), 5.04 (ddd, 1H, J = 11.5, 3.5, 1.0 Hz), 6.14 (d, 1H, J = 3.0 Hz), 6.20 (d, 1H, J = 2.0 Hz), 6.49 (t, 1H, J = 5.0 Hz), 7.03 (d, 1H, J = 1.5 Hz), 7.10 (dt, 1H, J = 8.0, 1.0 Hz), 7.17 (dt, 1H, J = 8.0, 1.0 Hz), 7.29 (d, 1H, J = 8.0 Hz), 7.49 (d, 1H, J = 7.5 Hz), 8.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.7, 24.3, 25.7, 26.3, 26.7, 36.2, 36.4, 37.5, 39.8, 43.3, 46.1, 47.2, 60.0, 107.2, 108.9, 110.3, 111.1, 118.3, 119.4, 122.1, 126.1, 135.7, 136.5, 142.1, 151.3, 170.7, 171.1, 172.1; HRMS (ESI) calculated for $C_{29}H_{35}N_4O_4$ 503.2658 $[M + H]^+$, found 503.2645.

Indoloquinolizidine 17h. It was prepared from indoloquinolizidine **10d** and amine **16g** in 15.0 mg, 71% yield by following the same protocol of **17a**. Pale yellow liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02−1.07 (m, 1H), 1.33−1.38 (m, 1H), 1.42−1.47 (m, 2H), 1.48−1.54 (m, 2H), 1.95−1.99 (m, 4H), 2.46 (dt, 1H, J = 14.0, 10.0 Hz), 2.59 (dd, 1H, J = 14.5, 4.5 Hz), 2.67−2.74 (m, 1H), 2.76−2.78 (m, 1H), 2.81 (dd, 1H, J = 15.0, 6.5 Hz), 2.89 (dd, 1H, J = 12.0, 4.0 Hz), 2.93−2.98 (m, 3H), 3.27−3.31 (m, 3H), 3.50−3.68 (m, 4H), 5.05 (ddd, 1H, J = 12.5, 4.0, 1.0 Hz), 6.71 (t, 1H, J = 5.0 Hz), 7.09 (t, 1H, J = 7.5 Hz), 7.13−7.17 (m, 3H), 7.28 (d, 1H, J = 8.0 Hz), 7.48 (d, 1H, J = 8.0 Hz), 7.60 (dt, 1H, J = 7.5, 1.5 Hz), 8.51 (dd, 1H, J = 5.5, 2.0 Hz), 8.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.8, 24.3, 25.7, 26.5, 26.8, 36.2, 37.0, 37.3, 38.7, 40.0, 43.2, 45.9, 47.2, 59.8, 108.9, 111.0, 118.3, 119.3, 121.6, 122.0, 123.3, 126.1, 135.6, 136.5, 136.6, 149.2, 159.4, 170.7, 171.1, 172.3; HRMS (ESI) calculated for $C_{31}H_{38}N_5O_3$ 528.2975 $[M + H]^+$, found 528.2968.

Indoloquinolizidine 17i. It was prepared from indoloquinolizidine **10h** and amine **16s** in 15.7 mg, 63% yield by following the same protocol of **17a**. Pale yellow liquid: ^{1}H NMR (500 MHz, CD_3OD) δ 1.68 (dt, 1H, J = 13.5, 4.5 Hz), 1.88 (s, 3H), 2.55−2.62 (m, 1H), 2.75−2.79 (m, 2H), 2.80−2.83 (m, 2H), 2.90−2.99 (m, 2H), 3.03−3.07 (m, 2H), 3.27−3.29 (m, 2H), 3.47−3.53 (m, 2H), 3.58−3.63 (m, 2H), 3.67−3.72 (m, 3H), 3.74−3.79 (m, 2H), 3.80−3.91 (m, 4H), 4.97 (dt, 1H, J = 12.5, 3.0 Hz), 6.60 (dd, 1H, J = 3.0, 1.5 Hz), 7.07−7.10 (m, 2H), 7.32 (d, 1H, J = 8.5 Hz), 7.45 (d, 1H, J = 2.0 Hz), 7.70−7.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 21.4, 27.5, 34.9, 36.6, 37.2, 41.5, 42.3, 45.4, 45.9, 46.4, 59.5, 66.7, 109.1, 111.5, 112.0, 117.2, 117.9, 122.3, 125.1, 127.1, 134.0, 137.7, 144.0, 147.5, 159.1, 169.9, 170.4, 172.9; HRMS (ESI) calculated for $C_{32}H_{37}N_5O_6Cl$ 622.2432 $[M + H]^+$, found 622.2437.

Indoloquinolizidine 17j. It was prepared from indoloquinolizidine **10m** and amine **16i** in 14.6 mg, 69% yield by following the same protocol of **17a**. Pale yellow liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (d, 1H, J = 6.5 Hz), 1.68−1.73 (m, 2H), 1.94 (s, 3H), 2.00−2.03 (m, 1H), 2.44−2.51 (m, 2H), 2.69−2.76 (m, 2H), 2.88−2.95 (m, 3H), 3.22−3.29 (m, 3H), 3.30 (s, 3H), 3.31−3.35 (m, 1H), 3.41 (t, 2H, J = 5.5 Hz), 3.44−3.48 (m, 1H), 3.49−3.57 (m, 2H), 3.60 (t, 2H, J = 5.5 Hz), 3.72−3.76 (m, 1H), 3.84 (s, 3H), 5.06 (dd, 1H, J = 12.5, 3.5 Hz), 6.33 (t, 1H, J = 5.0 Hz), 6.82 (dd, 1H, J = 9.0, 1.5 Hz), 6.92 (d, 1H, J = 1.5 Hz), 7.17 (d, 1H, J = 9.0 Hz), 8.52 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 21.8, 26.8, 29.2, 36.0, 37.3, 37.7, 39.8, 42.3, 45.8, 46.4, 55.9, 58.7, 59.7, 66.6, 66.7, 71.2, 100.3, 108.9, 111.8, 112.2, 126.3, 130.7, 137.1, 154.1, 170.5, 171.1, 172.7; HRMS (ESI) calculated for $C_{28}H_{39}N_4O_6$ 527.2870 $[M + H]^+$, found 527.2854.

Hydroxyindoline 11a. A solution of starting indoloquinolizidine **17a** (46.3 mg, 0.10 mmol) in CH_2Cl_2 (2.5 mL) was treated with oxaziridine **18** (63.2 mg, 0.32 mmol). The reaction mixture was stirred overnight at room temperature, and then solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (elution with EtOAc:MeOH = 4:1) to give hydroxyindoline **11a** (25.8 mg, 54%). Pale yellow amorphous solid: ^{1}H NMR (500 MHz, CD_3OD) δ 1.72 (s, 3H), 1.72−1.75 (m, 1H), 1.87 (ddd, 1H, J = 14.5, 8.0, 3.0 Hz), 2.43−2.47 (m, 1H), 2.48−2.52 (m, 1H), 2.70 (dt, 1H, J = 14.0, 9.0 Hz), 2.83 (s, 3H), 2.83−2.86 (m, 1H), 2.88−2.90 (m, 1H), 2.91 (s, 3H), 3.06−3.11 (m, 1H), 3.99 (dd, 1H, J = 11.0, 3.0 Hz), 4.33 (d, 1H, J = 15.5 Hz), 4.38 (d, 1H, J = 15.5 Hz), 4.62 (ddd, 1H, J = 14.0, 9.0, 3.0 Hz), 6.23 (dd, 1H, J = 3.0, 0.5 Hz), 6.33 (dd, 1H, J = 3.0, 1.5 Hz), 7.27 (dt, 1H, J = 7.5, 1.0 Hz), 7.36 (dt, 1H, J = 7.5, 1.0 Hz), 7.40−7.41 (m, 1H), 7.44 (d, 1H, J = 7.0 Hz), 7.46 (d, 1H, J = 7.5 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 20.6, 27.1, 34.9, 36.4, 36.7, 37.2, 37.9, 38.7, 40.0, 40.7, 65.1, 83.1, 108.1, 111.4, 121.8, 123.5, 128.3, 130.5, 143.3, 143.5, 153.0, 154.1, 172.5, 173.6, 187.7; HRMS (ESI) calculated for $C_{26}H_{31}N_4O_5$ 479.2294 $[M + H]^+$, found 479.2299. Single crystals for X-ray analysis were obtained by slow evaporation of saturated solution method. CCDC number is 791452.

Hydroxyindoline 11b. A solution of starting indoloquinolizidine **17b** (51.5 mg, 0.10 mmol) in CH_2Cl_2 (2.5 mL) was treated with oxaziridine **18** (63.2 mg, 0.32 mmol). The reaction mixture was stirred overnight at room temperature, and then solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (elution with EtOAc:MeOH = 4:1) to give hydroxyindoline **11b** (34.5 mg, 65%). Pale yellow amorphous solid: ^{1}H NMR (500 MHz, CD_3OD) δ 1.32 (s, 9H), 1.70−1.72 (m, 1H), 1.73 (s, 3H), 1.94 (ddd, 1H, J = 14.5, 8.0, 3.0 Hz), 2.42 (dd, 1H, J = 14.5, 10.0 Hz), 2.51−2.57 (m, 1H), 2.65−2.70 (m, 1H), 2.73 (dd, 1H, J = 14.5, 4.0 Hz), 2.89 (dt, 1H, J = 14.0, 8.0 Hz), 3.01−3.05 (m, 1H), 3.11−3.15 (m, 1H), 3.33−3.36 (m, 2H), 3.40−3.56 (m, 3H), 3.61−3.69 (m, 2H), 3.95 (dd, 1H, J = 11.5, 3.5 Hz), 4.59 (ddd, 1H, J = 14.0, 9.0, 3.0 Hz), 7.40 (dd, 1H, J = 8.0, 2.0 Hz), 7.45 (d, 1H, J = 2.0 Hz), 7.47 (d, 1H, J = 8.0 Hz), 7.67 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 20.1, 27.3, 28.9, 35.2, 36.8, 37.9, 40.1, 40.9, 43.7, 48.0, 52.2, 65.2, 67.5, 67.7, 83.3, 123.1, 124.2, 130.5, 134.1, 145.7, 152.6, 171.2, 173.1, 173.7, 187.9; HRMS (ESI) calculated for $C_{27}H_{36}N_4O_5Cl$ 531.2374 $[M + H]^+$, found 531.2366.

Hydroxyindoline 11c. A solution of starting indoloquinolizidine **17c** (43.9 mg, 0.10 mmol) in CH_2Cl_2 (2.5 mL) was treated with oxaziridine **18** (63.2 mg, 0.32 mmol). The reaction mixture was stirred overnight at room temperature, and then solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (elution with EtOAc:MeOH = 4:1) to give hydroxyindoline

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11c (31.4 mg, 69%). Pale yellow amorphous solid: ^{1}H NMR (500 MHz, CD_3OD) δ 1.32 (s, 9H), 1.72 (s, 3H), 1.72−1.73 (m, 1H), 1.85−1.90 (m, 1H), 2.39 (ddd, 1H, J = 14.5, 10.0, 2.0 Hz), 2.45−2.52 (m, 1H), 2.67−2.71 (m, 1H), 2.75 (ddd, 1H, J = 14.5, 4.0, 1.5 Hz), 2.84 (s, 3H), 2.86−2.90 (m, 1H), 2.92 (s, 3H), 3.03−3.05 (m, 1H), 3.99−4.02 (m, 1H), 4.59−4.64 (m, 1H), 7.26−7.29 (m, 1H), 7.35−7.38 (m, 1H), 7.44−7.47 (m, 2H), 7.68 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 20.5, 27.2, 28.9, 35.1, 36.4, 36.7, 38.0, 38.7, 40.7, 41.0, 52.0, 65.1, 83.1, 121.8, 123.5, 128.3, 130.5, 143.5, 154.1, 172.5, 173.2, 173.9, 187.7; HRMS (ESI) calculated for $C_{25}H_{35}N_4O_4$ 455.2658 $[M + H]^+$, found 455.2647.

Spirocyclic Dihydroindolone 12a. A solution of starting hydroxyindoline **11b** (5.10 mg, 9.6 μmol) in MeOH (0.6 mL) was treated with aqueous H_2SO_4 (0.2 mL, 10% v/v). The reaction mixture was stirred overnight at 40 °C and then diluted to 1.0 mL. The crude product was purified by LC−MS to give spirocyclic dihydroindolone **12a** (4.69 mg, 92%). Pale yellow amorphous solid: ^{1}H NMR (500 MHz, CD_3OD) δ 1.32 (s, 9H), 1.61 (d, 1H, J = 14.0 Hz), 1.72 (s, 3H), 2.01 (dd, 1H, J = 13.5, 8.5 Hz), 2.27−2.37 (m, 2H), 2.40 (dd, 1H, J = 15.0, 9.0 Hz), 2.64 (dd, 2H, J = 15.0, 4.0 Hz), 2.90−2.97 (m, 1H), 3.01−3.03 (m, 1H), 3.15 (dd, 1H, J = 13.0, 4.0 Hz), 3.20−3.23 (m, 1H), 3.34−3.39 (m, 5H), 3.61 (t, 1H, J = 11.0 Hz), 3.79−3.85 (m, 1H), 6.87 (d, 1H, J = 8.5 Hz), 7.37 (s, 1H), 7.42 (d, 1H, J = 9.0 Hz), 7.47 (s, 1H), 8.16 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 20.5, 28.2, 29.0, 29.8, 37.3, 38.6, 40.4, 42.4, 43.0, 47.7, 52.1, 67.2, 67.3, 67.6, 77.7, 115.0, 121.1, 124.1, 124.3, 138.9, 161.4, 171.7, 172.7, 172.8, 203.5; HRMS (ESI) calculated for $C_{27}H_{36}N_4O_5Cl$ 531.2374 $[M + H]^+$, found 531.2377. Single crystals for X-ray analysis were obtained by slow evaporation of saturated solution method. CCDC number is 791453.

Spirocyclic Dihydroindolone 12b. A solution of starting hydroxyindoline **11c** (4.38 mg, 9.6 μmol) in MeOH (0.6 mL) was treated with aqueous H_2SO_4 (0.2 mL, 10% v/v). The reaction mixture was stirred overnight at 40 °C and then diluted to 1.0 mL. The crude product was purified by LC−MS to give spirocyclic dihydroindolone **12b** (2.85 mg, 65%). Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.78 (s, 3H), 2.00−2.04 (m, 1H), 2.07 (ddd, 1H, J = 13.0, 8.0, 1.5 Hz), 2.20 (s, 3H), 2.22−2.30 (m, 2H), 2.36 (dd, 1H, J = 13.5, 5.0 Hz), 2.66 (s, 3H), 2.71 (dd, 1H, J = 13.5, 6.0 Hz), 2.86−2.88 (m, 1H), 2.93 (dd, 1H, J = 13.5, 5.0 Hz), 3.68 (t, 1H, J = 11.0 Hz), 3.94−4.00 (m, 1H), 4.78 (s, 1H), 6.26 (s, 1H), 6.82 (dt, 1H, J = 8.0, 0.5 Hz), 6.89 (d, 1H, J = 8.5 Hz), 7.41−7.44 (m, 1H), 7.55−7.57 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 20.5, 27.9, 29.0, 29.6, 35.6, 37.4, 38.0, 38.8, 40.8, 42.5, 52.1, 67.3, 76.8, 113.4, 119.2, 120.3, 124.9, 139.2, 163.1, 172.7, 172.9, 173.0, 205.1; HRMS (ESI) calculated for $C_{25}H_{35}N_4O_4$ 455.2658 $[M + H]^+$, found 455.2665.

Tricylic Ketoamide 13a. A solution of starting indoloquinolizidine **17b** (61.4 mg, 0.14 mmol) in CH_2Cl_2 (3 mL) was treated with *m*-CPBA (95.0 mg, 0.42 mmol). The reaction mixture was stirred for 30 min at room temperature, diluted with EtOAc (6 mL), washed with Na_2SO_3 (saturated solution, 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (elution with EtOAc:MeOH = 4:1) to give tricyclic ketoamide **13a** (46.8 mg, 71%). Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.44 (s, 3H), 2.12 (dt, 1H, J = 14.5, 4.5 Hz), 2.19 (dd, 1H, J = 16.0, 3.0 Hz), 2.33−2.40 (m, 1H), 2.82−2.87 (m, 1H), 2.94−2.98 (m, 4H), 3.03 (dd, 1H, J = 13.5, 6.5 Hz), 3.09 (dd, 1H, J = 14.5, 6.5 Hz), 3.17 (s, 3H), 3.25 (dd, 1H, J = 16.0, 6.0 Hz), 3.84 (dd, 1H, J = 9.0, 4.0 Hz), 4.54 (dd, 1H, J = 15.0, 11.0 Hz), 5.59 (s, 1H), 7.17 (d, 1H, J = 8.0 Hz), 7.41 (t, 1H, J = 7.5 Hz), 7.54 (dt, 1H, J = 7.5, 1.5 Hz), 7.61 (dd, 1H, J = 7.5, 1.5 Hz), 10.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 27.6, 28.7, 34.7, 36.2, 37.6, 38.9, 39.9, 40.7, 43.9, 52.0, 67.0, 127.8, 127.9, 128.8, 132.2, 136.7, 140.4, 170.5, 170.5, 171.9, 174.6, 204.5; HRMS (ESI) calculated for $C_{25}H_{35}N_4O_5$ 471.2607 $[M + H]^+$, found 471.2598. Single crystals for X-ray analysis were obtained by slow evaporation of saturated solution method. CCDC numer is 791450.

Tricyclic Ketoamide 13c. It was prepared in 16.9 mg, 32% yield by following the same procotol of **13a**. Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 3H), 2.22−2.27 (m, 1H), 2.27−2.31 (m, 2H), 2.81−2.83 (m, 1H), 2.90−2.94 (m, 1H), 2.95 (s, 3H), 3.03−3.05 (m, 1H), 3.06−3.08 (m, 1H), 3.13 (s, 3H), 3.32 (dd, 1H, J = 16.0, 6.0 Hz), 3.78 (dd, 1H, J = 7.5, 4.5 Hz), 4.20 (dd, 1H, J = 15.5, 5.0 Hz), 4.39 (dd, 1H, J = 15.5, 6.5 Hz), 4.54 (dd, 1H, J = 14.0, 4.0 Hz), 6.09−6.10 (m, 1H), 6.25−6.28 (m, 2H), 7.17 (d, 1H, J = 8.5 Hz), 7.30−7.31 (m, 1H), 7.50 (dd, 1H, J = 8.5, 2.5 Hz), 7.58 (d, 1H, J = 2.5 Hz), 10.4 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 27.3, 34.4, 36.2, 36.7, 37.7, 38.5, 38.8, 40.3, 43.8, 67.1, 107.8, 110.5, 128.9, 129.7, 132.1, 134.0, 135.2, 141.5, 142.3, 150.4, 170.4, 170.7, 172.3, 174.8, 203.0; HRMS (ESI) calculated for $C_{26}H_{30}N_4O_6Cl$ 529.1854 $[M + H]^+$, found 529.1861.

Pyrroloquinolone 14a. A solution of starting tricyclic ketoamide **13b** (33.8 mg, 0.062 mmol) in EtOH (1 mL) was treated with KOH (4.3 mg, 0.077 mmol). The reaction mixture was stirred overnight at room temperature, and then solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (elution with EtOAc:MeOH = 4:1) to give pyrroloquinolone **14a** (17.3 mg, 53%). Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 9H), 1.55−1.61 (m, 5H), 1.92 (s, 3H), 2.26−2.31 (m, 1H), 2.34 (dd, 1H, J = 14.5, 5.0 Hz), 2.38−2.46 (m, 1H), 2.89−2.92 (m, 1H), 2.97 (dd, 1H, J = 14.5, 4.5 Hz), 3.26 (dd, 1H, J = 13.5, 6.0 Hz), 3.39−3.48 (m, 3H), 3.59−3.62 (m, 1H), 3.74−3.77 (m, 1H), 4.55 (d, 1H, J = 15.0 Hz), 4.92 (d, 1H, J = 15.5 Hz), 5.95 (s, 1H), 7.28 (d, 1H, J = 9.0 Hz), 7.51 (dd, 1H, J = 9.0, 2.5 Hz), 8.33 (d, 1H, J = 2.5 Hz), 10.3 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 24.2, 25.8, 26.7, 26.9, 28.7, 35.5, 39.0, 43.5, 47.2, 47.3, 48.2, 51.1, 67.9, 113.3, 119.7, 125.3, 126.8, 129.7, 132.1, 138.1, 152.6, 169.2, 170.5, 171.3, 173.5; HRMS (ESI) calculated for $C_{28}H_{36}N_4O_4Cl$ 527.2425 $[M + H]^+$, found 527.2418. Single crystals for X-ray analysis were obtained by slow evaporation of saturated solution method. CCDC number is 791454.

Pyrroloquinolone 14b. It was prepared in 18.3 mg, 69% yield by following the same procotol of **14a**. Pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.90 (s, 3H), 2.26 (dt, 1H, J = 12.5, 5.0 Hz), 2.33 (dd, 1H, J = 14.5, 4.5 Hz), 2.41−2.48 (m, 1H), 2.86−2.89 (m, 1H), 3.01 (dd, 1H, J = 15.0, 4.5 Hz), 3.35 (dd, 1H, J = 13.5, 6.0 Hz), 3.56−3.60 (m, 2H), 3.64−3.66 (m, 2H), 3.70−3.73 (m, 2H), 3.75−3.79 (m, 2H), 4.54 (d, 1H, J = 15.0 Hz), 4.90 (d, 1H, J = 15.0 Hz), 5.88 (s, 1H), 7.28 (s, 1H), 7.49 (dd, 1H, J = 9.0, 2.5 Hz), 8.29 (d, 1H, J = 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 27.1, 28.7, 35.3, 38.9, 42.6, 46.7, 46.7, 48.2, 51.1, 66.7, 66.8, 67.7, 113.3, 119.8, 125.2, 126.7, 129.7, 132.1, 138.1, 152.4, 169.0, 170.6, 172.0, 173.4; HRMS (ESI) calculated for $C_{27}H_{34}N_4O_5Cl$ 529.2218 $[M + H]^+$, found 529.2205.

Syntheses of 476-Member Library of Indoloquinolizidines 17. Forty quinolizidine-containing carboxylic acids **10** were coupled with 12 amines **16** (1.5 equiv) and then treated with HATU (1.5 equiv), and DIPEA (3 equiv) in DMF. The reaction mixtures were stirred overnight at room temperature. The 480 crude mixtures were purified by preparative LC−MS to give 476 indoloquinolizidines **17** with an average yield of 20 mg (65%) and greater than 95% purity.

Syntheses of 96-Member Library of Indoloquinolizidines 17. Eight quinolizidine-containing carboxylic acids **10** were coupled with 12 amines **16** (1.5 equiv) and then treated with HATU (1.5 equiv), and DIPEA (3 equiv) in DMF. The reaction mixtures were stirred overnight at room temperature. The 96 crude mixtures were purified by preparative LC−MS to give 96 indoloquinolizidines **17** with an average yield of 58 mg (74%) and greater than 95% purity. The products were then split into two sets of vials for different diversification pathways.

Syntheses of 83-Member Library of Spirocyclic Dihydroindolones 12. Ninety-six indoloquinolizidines **17** were treated with oxaziridine **18** (3 equiv) in CH_2Cl_2. The reaction mixtures were stirred overnight at room temperature. The 96 crude mixtures were purified by preparative LC−MS to give 96 hydroxyindolines **11**, which were immediately dissolved in MeOH and treated with aqueous H_2SO_4 (10% v/v). The reaction mixtures were stirred overnight at 40 °C and then diluted by water. The 96 crude mixtures were purified by preparative LC−MS to give 83 spirocyclic dihydroindolones **12** with

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an average yield of 7 mg (30%) after two steps and greater than 95% purity.

Syntheses of 96-Member Library of Tricyclic Ketoamides 13. Ninety-six indoloquinolizidines **17** were treated with *m*-CPBA (3 equiv) in CH_2Cl_2. The reaction mixtures were stirred for 30 min at room temperature, diluted with EtOAc, and washed with Na_2SO_3 (saturated solution) and brine. The 96 crude mixtures were purified by preparative LC−MS to give 96 tricyclic ketoamide **13** with an average yield of 11 mg (47%) and greater than 95% purity. The products were then split into two sets of vials for final diversification.

Syntheses of 96-Member Library of Pyrroloquinolones 14. Ninety-six tricyclic ketoamides **13** in EtOH were treated with KOH (1.0 equiv). The reaction mixtures were stirred overnight at room temperature. The 96 crude mixtures were purified by preparative LC−MS to give 96 pyrroloquinolones **14** with an average yield of 5 mg (64%) and greater than 95% purity.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, crystal data (CIF), and analytical and spectral characterization data for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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