Probing Chemical Space with Alkaloid-Inspired Libraries

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Abstract

Screening of small molecule libraries is an important aspect of probe and drug discovery science. Numerous authors have suggested that bioactive natural products are attractive starting points for such libraries, due to their structural complexity and sp^3-rich character. Here, we describe the construction of a screening library based on representative members of four families of biologically active alkaloids (Stemonaceae, the structurally related cyclindricine and lepadiformine families, lupin, and Amaryllidaceae). In each case, scaffolds were based on structures of the naturally occurring compounds or a close derivative. Scaffold preparation was pursued following the development of appropriate enabling chemical methods. Diversification provided 686 new compounds suitable for screening. The libraries thus prepared had structural characteristics, including sp^3 content, comparable to a basis set of representative natural products and were highly rule-of-five compliant.

Natural products (NPs) have played a central role in medicine for as long as humans have sought to cure and ameliorate disease[1,2]. Many have been fine-tuned by evolution for purposes that bear a mechanistic relationship to a given therapeutic need[3]. NPs are often potent, selective, and able to cross biological membranes although many do not adhere to common paradigms for oral absorption[4] (it is worth recalling that NPs were specifically excluded from Lipinski's guidelines of drug-like properties[5]). For these reasons, NPs continue to inspire creativity in both medicinal chemistry and chemical synthesis.

As screening of small molecule libraries remains an important aspect of early stage drug and probe discovery, there has been interest in increasing the representation of NPs and related structures in libraries[6-10]. Approaches include the straightforward approach of collecting NPs or NP extracts from their natural sources, which requires access to libraries obtained from bioprospecting and, for extracts, a downstream deconvolution step. To supplement such sources, synthetic chemists have co-opted NP structures for construction of NP-like libraries. More often than not these efforts provide purpose-built libraries for biological

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indications closely related to known bioactivities of the NP itself[11-13]. Diversityoriented synthesis (DOS) has also been used to create NP-inspired libraries[9,14,15]. Some authors suggested that the higher sp^3/sp^2 content and rich stereochemistry typical of NPs and, by extension, libraries derived from them is correlated with suitability as drug candidates[16-20]. In all of these approaches, the complexity of NPs presents synthetic challenges that must be surmounted to provide screening libraries that contain chemotypes that can be modified in the case of attractive hits[21,22].

We sought an approach to NP-like screening libraries that would balance the likelihood of finding molecules useful in the pursuit of new biology with synthetic tractability. We chose to focus on selected families of alkaloids, preferring those with established biological activity at multiple targets, hypothesizing that such families might embody a "privileged structure"[23-28] that could be optimized for new biological properties following suitable modification. Thus, we created a nested set of synthetically derived cores that represented salient structural features of the NP starting point. These were further modified to produce "secondary scaffolds" that differ more substantially from the original structure but retain attractive elements of scaffold design. In previous work, we used these tenets to create a library based on Stemonaceae alkaloids that ultimately led to potent Sigma–1 ligands, an activity not known to be associated with this family of NPs[29].

Here, we generalize this concept to structurally diverse alkaloids of the cylindricine, Amaryllidaceae, and lupin families. We sought to address the synthetic challenges presented by these families by repurposing a suite of thematically related chemical reactions to library construction, most of which were developed in the context of total synthesis. Additional method development ultimately allowed us to obtain diversifiable scaffolds unavailable directly from NP starting materials. Overall, we synthesized a total of 686 new compounds, of which >90% were prepared in >20 mg quantities and all in >90% purity.

Figure 1 depicts scaffolds inspired by the architecture of four biologically active alkaloid families: (1) Stemonaceae alkaloids (exemplified by neostenine)[30,31] (2) the structurally related cylindricine, lepadiformine, and fascicularine families of marine alkaloids (here, collectively called the cylindricine series)[32], (3) the Amaryllidaceae alkaloid mesembrine[33], and (4) sparteine, a lupin alkaloid[34,35]. Structurally, each starting alkaloid contains at least one fused pair of rings, but one spiro and one bridged ring system are also represented. Biologically, these classes represent a variety of reported activities, ranging from those described in traditional medicine for the NP source to pharmacologically verified and clinically used agents (**Supplementary Table 1**). According to the approach outlined above, each polycyclic alkaloid was simplified to the primary and secondary scaffolds indicated (**Fig. 1**). The secondary scaffolds contain the same number of rings as the central scaffold, but with different ring sizes and/or connectivities.

RESULTS

Synthesis of scaffolds

To make libraries containing 40–320 members each, it was necessary to develop enabling chemistries that would permit practical access to the desired chemotypes (**Fig. 2**). This was

pursued using the azido-Schmidt conversion of keto azides to lactams as the primary unifying technology[36]. Four variations of this reaction were used to create the desired scaffolds: (1) the combined Diels–Alder/Schmidt reaction between a silyloxy diene and an azide-containing dienophile[37] (Stemonaceae alkaloid series and one scaffold for the mesembrine series; **Fig. 2a, d**), (2) the reaction of a ketone with a hydroxylalkyl azide[38] (cylindricine series; **Fig. 2b**), (3) the intramolecular Schmidt reaction of a ketone tethered to an azide[39] (sparteine series; Fig. 2c), and (4) another combined Diels–Alder/Schmidt reaction, but this time one in which the azide is attached to the diene (the second mesembrine scaffold; **Fig 2d**).

The Diels–Alder/Schmidt sequence is particularly powerful as it extends the applicability of the ubiquitous Diels–Alder reaction by tying it to the in situ conversion of the new ring into a heterocycle. The other sequences rely in one case (**Fig. 2b**) on a spiroannulation step to afford a cyclobutanone (itself pressed into service as a scaffold; see below) that can be converted into the desired spirocyclic intermediates. Finally, the route in **Fig. 2c** parlays an advanced total synthesis intermediate into the scaffold **16**. To use the Diels–Alder/Schmidt chemistry in panels **a** and **d**, we needed to explore new variations using highly substituted dienes. Schmidt reactions related to those shown in panels **b** and **c** were first developed during total synthesis efforts toward lepadiformine and cylindricine alkaloids[39,40]. The azido alcohol-mediated Schmidt reaction has been previously used for building a library of γ-turn mimetics[41]. We prepared most of the scaffolds in racemic form as there was no reason to favor a particular enantiomer for broad screening, often in straightforward biochemical assays (in a few cases, we did make scaffolds from L-configured amino-acid derivatives).

The Lewis acid-promoted reaction of unsubstituted diene **1a** with **2** was previously reported[37] but dienes **1b-d**, which contain an additional element of diversity and are readily prepared in   3 steps from commercially available starting material, were unknown to engage in Diels–Alder/Schmidt chemistry prior to this work. All four dienes underwent the desired conversions, which were reproducible and scalable to provide up to 12 g of lactam with no loss of efficiency. Mechanistically, such reactions are believed to proceed by a Diels–Alder reaction, from which the product stereochemistry arises, followed by an intramolecular Schmidt reaction[37]. The relative stereochemistries of lactams **3b-d** were confirmed by X-ray crystallography. Reductive amination with ammonium acetate provided amines **4a-d** in good yield in 2–6:1 dr; the diastereomers of amines **4b-d** were separated by reverse phase chromatography (the isomers of **4a** were inseparable and not used for library synthesis). The relative stereochemistry of **4b** and **4c** was confirmed by X-ray crystallography of sulfonamide derivatives (**Supplementary Information**) and amine **4d** was assigned by analogy.

Trost spiroannulation was used to create spirocyclic ketones **6a-h** (**Fig. 2b**)[42]. Once in hand, these ketones were used as the basis of one sublibrary but our main objective was to convert them to the cylindricine-inspired substructures **8** and **9**. This was accomplished by previously unexamined Schmidt reactions of **6a-h** with hydroxyalkyl azides **7a-d**. This led to a mixture of readily separable lactam regioisomers **8** and **9**, thus affording a pair of useful scaffolds from ketones **6**. The use of a two-carbon hydroxyalkyl azide led predominantly to

formation of scaffolds **8**, whereas three-carbon homologues afforded ca. 1:1 mixtures of constitutional isomers. Previous work has shown the selectivity of such reactions to be highly substrate-dependent; a discussion of the relevant topics has been published[38]. Additionally, lactams **8** and **9** were reduced to afford tertiary amine cores **10** and **11**.

The tricyclic lactam core of the sparteine–inspired scaffolds (**Fig. 2c**) was prepared by intramolecular Schmidt reaction of azide **12**, an intermediate in the total synthesis of sparteine[39]. Scale-up to 4.5 g quantities was possible by optimizing the previous route to compound **12**. The multistep reduction shown in the scheme afforded amines **15a-c** as single diastereomers, and further reduction with NaBH$_4$ similarly led to isomerically pure alcohols **16a-c**. The stereochemistry of the endo–selective Grignard addition and ketone reduction was confirmed by X-ray crystallography of a derived carbamate (see **Supplementary Information**).

The primary scaffold of the mesembrine series **18** was prepared in moderate yield and 3:1 to 4:1 dr by reacting previously unknown dienes **17** with methylvinylketone. These isomers proved inseparable and were not subjected to additional diversification. We similarly prepared secondary scaffold **21** by a modification of the previously reported Diels-Alder/ Schmidt reaction of diene **20** and azide-tethered enone **19** (**Fig. 2d**)[37]. Attaching the azide to either the diene or dienophile allows access to either the *cis* or *trans* fused scaffold, (cf. routes to **18** vs. **21**). Hypothesizing that greater selectivity might be obtained with a more biased ring system we reacted **17** with the unusual dienophile cyclobutenone (introduced to the Diels–Alder reaction by Danishefsky[43]), but a complex mixture of products was obtained, with no desired lactam evident. For comparison, we prepared azide-less silyloxydiene **22** and submitted it to the Diels-Alder reaction conditions with cyclobutenone. In this case, the cycloaddition proceeded smoothly to afford bicyclic ketone **23** but surprisingly treatment with trifluoromethanesulfonic acid resulted in the formation of the previously unknown isochromenones **24** as single diastereomers. This reaction is previously unknown and could proceed via a retro-Michael reaction from the intermediate shown (an alternative enolization/electrocyclic ring-opening sequence is also possible but available evidence does not currently allow us to differentiate between the possibilities).

Library construction

We took three main tacks toward diversifying our scaffolds: direct conversion of ketones to additionally fused heterocycles or amines, conversion of alcohols to carbamates, or decoration of amines as amides, sulfonamides, or ureas. These methods were chosen because they increase structural diversity, provide various degrees of hydrogen-bonding capabilities, and yield functional groups consistent with probe or drug development.

For the Stemonaceae-derived library, scaffold **3a** gave quinolines **25** by a modified Friedländer reaction and secondary amines **26** by reductive amination with various benzylamines (**Fig. 3a**). The analogous reactions with scaffolds **3b-d** resulted in an inseparable mixture of diastereomers, which were not pursued. Further diversification was achieved by reducing ketones **3a-d** with L-Selectride→ to generate the corresponding alcohols with excellent diastereoselectivity (relative stereochemistry of the major product

was determined by X-ray crystallography); these were used to prepare a library of carbamates **27**. Direct reaction of the alcohol with isocyanates resulted in the formation of an unidentified by-product that co-eluted with the carbamate product upon purification. However, by first converting the alcohol to the corresponding *para*-nitrobenzyl carbonate, subsequent reaction with a wide range of amines resulted in a much cleaner and more effective preparation of library members. Amine scaffolds **4b-d** were used to synthesize sublibraries of amides **28**, sulfonamides **29**, ureas **30** and secondary amines **26**, while tertiary amine libraries were obtained either by reductive amination of secondary amines **26** with formaldehyde, or by Eschweiler-Clarke reaction of primary amines **4b-d**.

Spirocyclic ketone scaffolds **6** were converted into libraries of amines **33** by microwave-assisted reductive amination, and libraries of carbamates **34** by reduction with NaBH$_4$ followed by reaction with isocyanates (**Fig. 3b**). Similarly, the alcohol moiety of lactams **8** and **9** and cyclic amines **10** and **11** were reacted with isocyanates and isothiocyanates to produce libraries of carbamates **35** and **36** and thiocarbamates **37** and **38**, respectively.

The ketone of scaffold **13** was stereoselectively reduced to afford the corresponding endo alcohol (**Fig. 4a**), the structure of which was determined by X-ray of the corresponding para-bromobenzoyl ester (see **Supplementary Information**). The alcohol was converted into a library of carbamates **40** by carbonate formation and subsequent reaction with a range of amines. The corresponding library containing a basic amine in the ring system was prepared by double reduction with LiAlH$_4$ in THF, giving **41**, which was further diversified into carbamates **42** by microwave-promoted reaction with isocyanates. Similar treatment of 16a-c led to libraries exemplified by **43**.

Reductive amination of mesembrine-inspired scaffold **19** provided the corresponding secondary amines **44** in 2:1 to 1:1 dr (**Fig. 4b**). We ascribe the poor stereoselectivity to the relatively flat nature of the *trans* ring-fused system inherent in **19**. In this case, the amine diastereomers were separable by reverse phase chromatography, which allowed us to incorporate a modest number of amines containing this scaffold into our library (relative stereochemistries were determined by 2D NMR). The use of anilines in the reductive amination resulted in inseparable mixtures of diastereomeric products, which were unsuitable for our screening requirements. A library of quinolines **45** was also synthesized by reacting scaffold **19** with either substituted 2-aminobenzaldehydes or 2-aminobenzophenones or acetophenones.

Cheminformatic analysis

The chemical properties of our alkaloid-inspired libraries were analyzed using principal component analysis (PCA), a statistical tool to condense multi dimensional chemical properties (e.g., MW, logP, ring complexity) into single dimensional numerical values (principal components), allowing greater ease of comparison with different sets of compounds[44]. This analysis was performed on a representative sample of scaffolds and library members summarized in **Fig. 5** (full list in **Supplementary Figs. 3 and 4**), which compared them to a selection of alkaloid NPs and a reference set of drugs, NPs, and commercial drug-like compounds using the protocols employed by Tan[45]. The parameters

that have the greatest influence on principal component 1 (PC1) are molecular weight, number of oxygen atoms, number of hydrogen bond acceptors, and topological polar surface area (tPSA). Together, these parameters have the effect of moving compounds to the right in plots PC1 v PC2 and PC1 v PC3. The descriptors with the largest loading on PC2 are the number of nitrogen atoms, number of aromatic rings, and the number of ring systems, which shift compounds upward in plots PC1 v PC2 and PC2 v PC3. In contrast, the nStMW parameter (defined as the number of $R – S$ stereocenters, this may be viewed as a rough descriptor of stereochemical complexity), shifts compounds downward in these plots. Finally, PC3 is affected to the greatest degree by XLogP (calculated octanol/water partition coefficient), number of rings, and ALOGPs (an alternative logP calculation), which together shift compounds in a negative direction along the PC3 axis in plots PC1 v PC3 and PC2 v PC3, and ALOGpS (calculated aqueous solubility), which shifts compounds in a positive direction in these plots.

In two of the three variations, the data show significant overlap between our alkaloid-inspired library compounds with both drug and NP regions (**Fig. 6a,b**). In the PC2 vs. PC3 plot, there is less overlap between our library compounds and commercial drug space, but the compounds still overlap considerably with natural alkaloid space and abuts drug space (**Fig 6c**). This might be expected to naturally arise from the combination of two different modes of synthetic chemistry: the natural-product inspired routes that led to the key scaffolds vs. the diversity generating steps that followed in the library expansion phase.

Principal moment of inertia (PMI) analysis[46] was also used to compare the 3-dimensional shapes of the lowest energy conformations of our scaffolds and library members with the above reference sets[45]. Our compounds were found to lie along the roddisc side of the triangle, with a preference for the rod vertex (**Fig. 6d**). We note that drugs and the commercially screening libraries represented in the reference sets also reside in this region of the plot[46].

These analyses suggest that our scaffolds and library compounds are similar to NPs, particularly alkaloid NPs, while also sharing attractive properties of drugs believed to be compatible with bioavailability. We note that the fraction of carbon atoms with an sp^3 center (Fsp^3) in our scaffolds (0.77) and library compounds (0.66) is very similar to the values obtained for our reference NPs (0.64) and alkaloids (0.65), and substantially higher than that for drugs (0.41) (**Supplementary Table 2**). Alkaloids (average MW 319, rotatable bonds 2.8) are generally smaller and more rigid than non-alkaloid NPs (629, 9.7), and more closely resemble our library compounds (355, 4.1). Although we did not particularly set out to adhere to any filters for drug-likeness in our design, we point out that 72% of our library compounds satisfied each of Lipinski's rules of 5, with 100% meeting 3 out of 4 of the criteria. Moreover, all library members fulfilled Veber's requirements for good oral bioavailability (10 rotatable bonds; 140 Å2 total polar surface area)[47].

DISCUSSION

We have described one approach to balancing two concerns that arise in the development of libraries for biological screening: (1) the desire to provide compound collections that are different enough from existing libraries to inform interesting new biology while (2) dealing

with the sheer vastness of chemical space, which makes it hard to create useful new bioactive molecules that are strikingly different from typical drug-like libraries. Using four alkaloids as inspiration agents, we used straightforward reaction sequences and moderately advanced synthetic intermediates to generate scaffold structures that were easily converted to libraries using parallel synthesis technology. The particular routes combine azide-mediated methods for the incorporation of nitrogen into organic frameworks with established ketone syntheses. Regarding the latter, we used one very well known reaction for the generation of fused ring systems (the Diels–Alder) and a powerful but somewhat underutilized method for generating spirocycles (the Trost spiroannulation). Overall, a total of 686 previously unknown structures were synthesized, comprising 55 separate scaffolds and 631 analogues. Of these, 266 (39%) of the compounds contained a basic nitrogen atom (ranges: 21% for the Stemonaceae alkaloid libraries to 68% of those derived from mesembrine). Overall, >90% of the library members were obtained in the 20 mg quantities and 90% purities that we had initially targeted (with the remainder achieving the purity goal but only being obtained in 10–20 mg quantities), with all of the compounds being >90% diastereomerically pure. The synthetic routes developed are amenable with both hit re-synthesis and downstream structure–activity relationships studies, both critical for real-world applications of small-molecule libraries.

The computational assessment of our libraries shows that the new compounds have many of the attributes that some authors have proposed to arise from using NPs in the first place, notably high sp^3 counts relative to commercial libraries and comparable to those in a previously used NP set[48]. This feature naturally arose from the selection of alkaloid-based scaffolds and reflects the choice of targets in the first place. In fact, the slight drop in average sp^3 content in the libraries made vs. the scaffolds themselves can be attributed to our selection of common "medicinal chemistry" subunits (e.g., aromatics) for our specific diversification efforts. On the other hand, the observation that the libraries were highly Lipinski- and Veber-compliant may be viewed as a surprise, given the conventional viewpoint that NPs have very different chemical properties from synthetically derived drug scaffolds. Overall, the PCA and PMI analysis support that the primary goal of this project was achieved insofar as we created libraries different enough from highly occupied drug discovery space to be interesting (and thus addressing our mission of "probing chemical space"), but not so different as to lack potential in screens. The ultimate determination of this potential through screening against a variety of targets (e.g., by submission into the Small Molecule Repository of the US National Institutes of Health) and the extension of the concept to other libraries are currently being pursued.

METHODS

General procedures for the key Schmidt reactions employed in the syntheses of scaffolds **3, 8, 9, 13, 18** and **21** are described below. All reactions were performed using flame-dried glassware under an argon atmosphere. Additional experimental details and analytical data for scaffold synthesis and library preparation are in the Supplementary Methods, along with full details of the cheminformatic analysis. CAUTION: The authors remind all experimentalists contemplating use of these methods to follow established safety protocols in the use of alkyl azides and their precursors.

General procedure for Diels-Alder/Schmidt reaction for preparation of scaffolds 3 (Stemonaceae alkaloid series)

Titanium tetrachloride (1 M solution in dichloromethane, 2.5 equiv.) was added dropwise to a solution of azide **2** (1 equiv.) and silyloxydiene **1a-d** (2.5 equiv.) in anhydrous dichloromethane (0.06 M w.r.t. azide) at 0 °C under argon. The resulting red/brown solution was stirred at 0 °C for 2 h, then allowed to warm slowly to room temperature overnight. The reaction mixture was then quenched with water and stirred at room temperature for 1 h. The organic layer was removed, and the aqueous extracted with dichloromethane (×3). The combined organics were dried (Na_2SO_4) and concentrated to afford a brown oil. The crude product was purified by chromatography (silica gel, 95:5 ethyl acetate: methanol) to afford lactams **3a-d**.

General procedure for azido-alcohol Schmidt reaction for preparation of scaffolds 8 and 9 (cylindricine series)

Boron trifluoride diethyl etherate (5 equiv.) was added dropwise to a solution of spiro[3.5]nonan-1-one **6a-h** (1 equiv.) in anhydrous dichloromethane (0.15 M w.r.t. spirononanone) at −78 °C under argon. The reaction mixture was stirred for 30 min at −78 °C, then a solution of hydroxyalkyl azide (3 equiv.) in dichloromethane (1.5 M) was added. The reaction mixture was stirred at −78 °C for 3 h, then allowed to warm slowly to room temperature overnight. The reaction mixture was then concentrated under reduced pressure and the resulting oil was dissolved in 15% aqueous potassium hydroxide solution and stirred for 30 min. The reaction mixture was then extracted with dichloromethane (×3). The combined organics were washed with water, dried ($MgSO_4$) and concentrated. The crude product was purified by automated chromatography (silica column, 0–100% ethyl acetate in hexanes) to afford lactams **8** and **9**.

Alkyl azide Schmidt reaction for preparation of scaffold 13 (sparteine series)

Titanium tetrachloride (20.7 mL, 188.5 mmol, 5 equiv.) was added dropwise to a solution of azide **12** (10 g, 37.7 mmol, 1.0 equiv.) in anhydrous dichloromethane (350 mL) at 0 °C under argon. A yellow precipitate was formed. The reaction mixture was allowed to warm to room temperature and stirred for 24 h, and then quenched with water. The aqueous layer was extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by chromatography (silica gel, 100% ethyl acetate) to afford lactam **13** (4.5 g, 62%) as a colorless solid.

General procedure for Diels-Alder/Schmidt reaction for preparation of scaffolds 18 (mesembrine series)

Methyl vinyl ketone (1 equiv.) was added to a solution of silyloxydiene **20** (1.5 equiv.) in anhydrous dichloromethane (0.4 M w.r.t. diene) and the reaction mixture cooled to −78 °C. Boron trifluoride diethyl etherate (1.5 equiv.) was then added and the reaction mixture stirred at −78 °C for 4 h then warmed to room temperature. A further aliquot of boron trifluoride diethyl etherate (2 equiv.) was then added and the reaction mixture stirred at room temperature for an additional 16 h. The reaction mixture was diluted with dichloromethane and quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with

saturated aqueous NH_4Cl, water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by automated column chromatography (silica column, 0 to 100% ethyl acetate in hexanes, then 90:10 dichloromethane:methanol) to afford lactams **18**.

Diels-Alder/Schmidt reaction for preparation of scaffold 21 (mesembrine series)

Ethylaluminium dichloride (1 M solution in hexane, 25 ml, 1 equiv.) was added dropwise to a solution of trimethylsilyloxy butadiene **20** (3.5 g, 25 mmol, 2.5 equiv.) and azide **19** (1.4 g, 10 mmol, 1 equiv.) in anhydrous dichloromethane (15 mL) under argon at −78 °C. After the addition was complete, the reaction mixture was stirred at −78 °C for 2 h then gradually warmed to room temperature and stirred for a further 16 h, then quenched with water and diluted with dichloromethane (100 mL). The combined organics were washed with saturated aqueous NaHCO3 (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography (silica column, 100% ethyl acetate) to afford lactam **19** (800 mg, 45%) as a light yellow oil.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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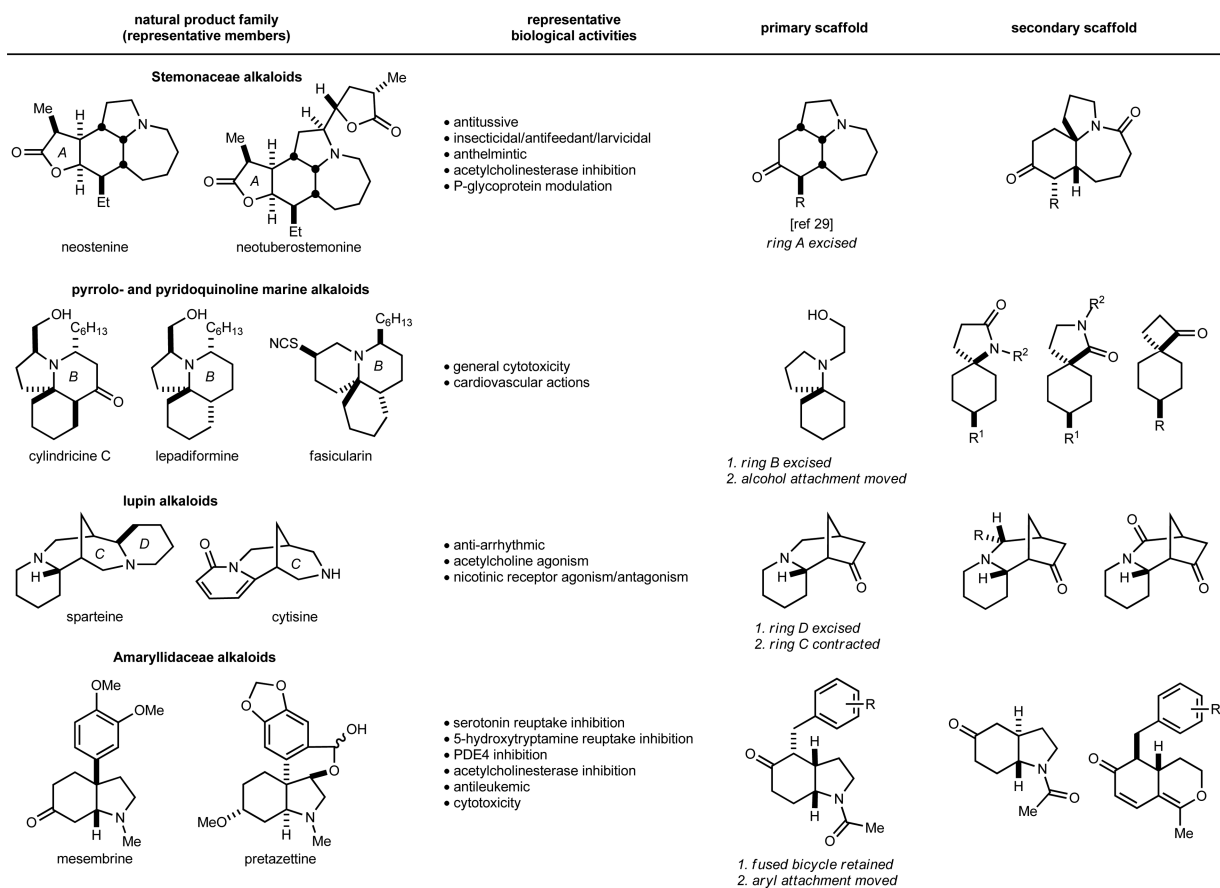
Figure 1. Strategic overview of NP families selected for library expansion and corresponding scaffold selection

Each family of NPs is exemplified by 2–3 members and the biological activities cited are representative of each family as a whole. The reviews[30-35] provide overviews of the biological landscape, with additional references provided in **Supplementary Table 1**. In each case, a primary scaffold embodies the minimal structural aspects of the NP family that were pursued. These involved removal of some features to enhance both versatility and synthetic accessibility. Secondary scaffolds (far right) represent more substantially modified variants of the primary scaffold, either through functional group or substitution changes or modification of ring structures.
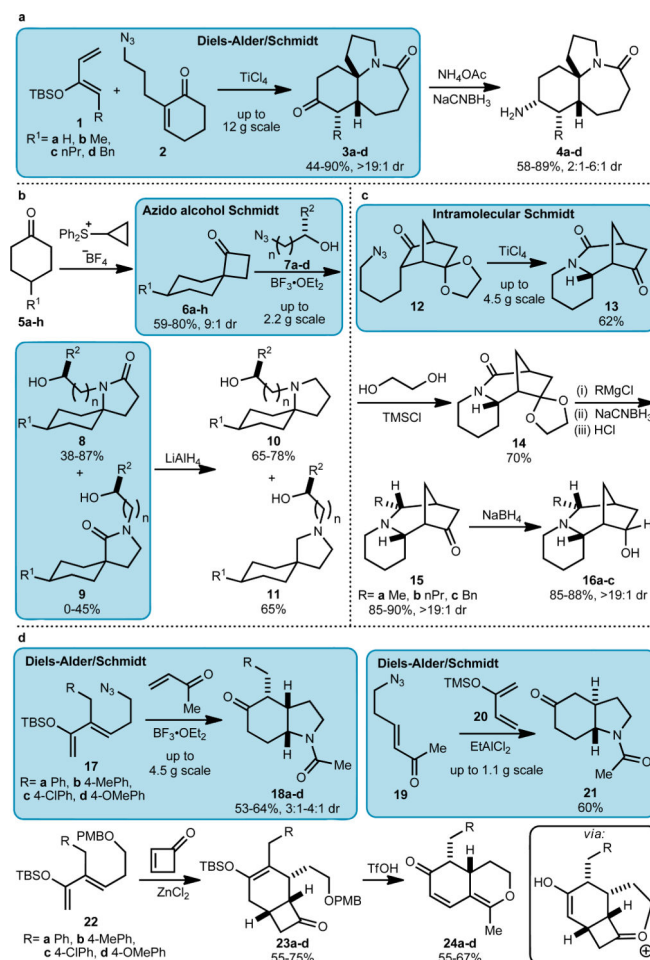
Figure 2. Construction of primary and secondary scaffolds

In each section, colored boxes indicate enabling chemistry developed for scaffold syntheses. (**a**) Synthesis of Stemonaceae alkaloid scaffolds using a Diels-Alder/Schmidt reaction. (**b**) Cylindricine scaffolds were prepared by sulfur ylide-mediated spiroannulation followed by ring expansion using an azido alcohol variant of the Schmidt reaction. (**c**) Azide **12** was prepared from a previously reported *C*2-symmetrical diketone[39] using an improved method (**Supplementary Information**) and converted to the tricyclic sparteine scaffolds using the intramolecular Schmidt reaction. (**d**) Two different variations of bicyclic analogs of mesembrine were prepared using a Diels-Alder/Schmidt reaction. In addition, reaction of **22** with the interesting dienophile cyclobutenone[43] followed by rearrangement afforded a non-nitrogenous scaffold **24**. Full synthetic schemes, including experimental details and characterization data of representative compounds, are available in the Supplementary Information accompanying this paper.
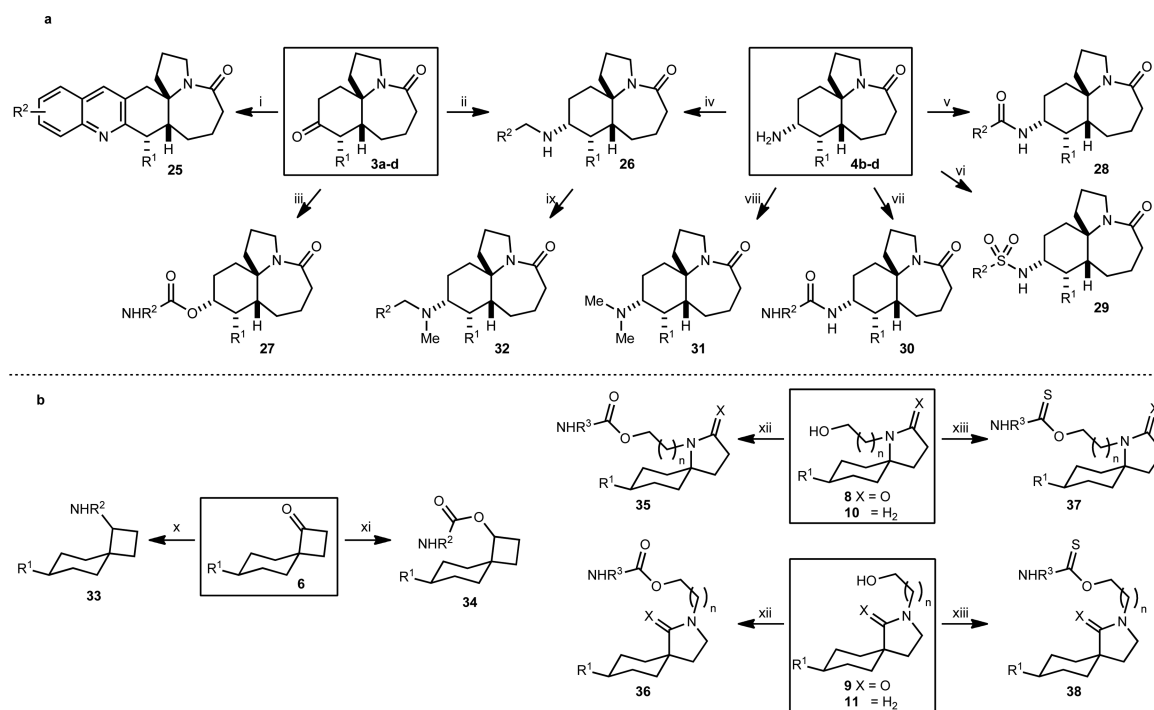
Figure 3. Library construction from Stemonaceae and cylindricine alkaloidinspired scaffolds
(**a**) Ketone scaffolds **3a-d** and amines **4b-d** were converted into libraries of quinolines, amines, amides, sulfonamides, ureas and carbamates; the key scaffolds are indicated by boxes. (**b**) Ketone scaffolds **6**, lactams **8** and **9**, and amines **10** and **11** were converted into a series of libraries of amines, carbamates and thiocarbamates. A total of 499 unique structures, each obtained in >90% purity (HPLC, UV detector at 214 nm) and >20 mg quantities were obtained. Scaffold (number of final products obtained): **3a-d** (131), **4c-d** (191), **6** (112), **8** (19), **9** (12), **10** (32), **11** (2). (i) 2-Nitrobenzaldehyde, Fe^0, 0.1 M aq HCl, EtOH, 85 °C; then **3a-d**, KOH, 85 °C; (ii) amine, AcOH, Na(OAc)$_3$BH, CH$_2$Cl$_2$, rt; (iii) a) L-Selectride, THF, −78 °C to rt, 90–95%, 9:1– 19:1 dr, (b) 4-nitrophenylchloroformate, pyridine, rt, 55–76%, (c) R^2NH_2, CH$_2$Cl$_2$, rt; (iv) R^2CHO, AcOH, Na(OAc)$_3$BH, CH$_2$Cl$_2$, rt; (v) R^2CO_2H, EDC, DMAP, CH$_2$Cl$_2$, rt; (vi) R^2SO_2Cl, Et$_3$N, CH$_2$Cl$_2$, rt; (vii) $R^2N{=}C{=}O$, PhMe, rt; (viii) H$_2$C=O, HCO$_2$H, 95 °C; (ix) H$_2$C=O, AcOH, Na(OAc)$_3$BH, CH$_2$Cl$_2$, rt; (x) R^2NH_2, DCE, microwave, 150 °C; (xi) a) NaBH$_4$, THF, MeOH, rt, 94–97%, (b) $R^2N{=}C{=}O$, Et$_3$N, THF, rt; (xii) $R^2N{=}C{=}O$, Et$_3$N, THF, rt; (xiii) $R^2N{=}C{=}S$, NaH, THF, rt.
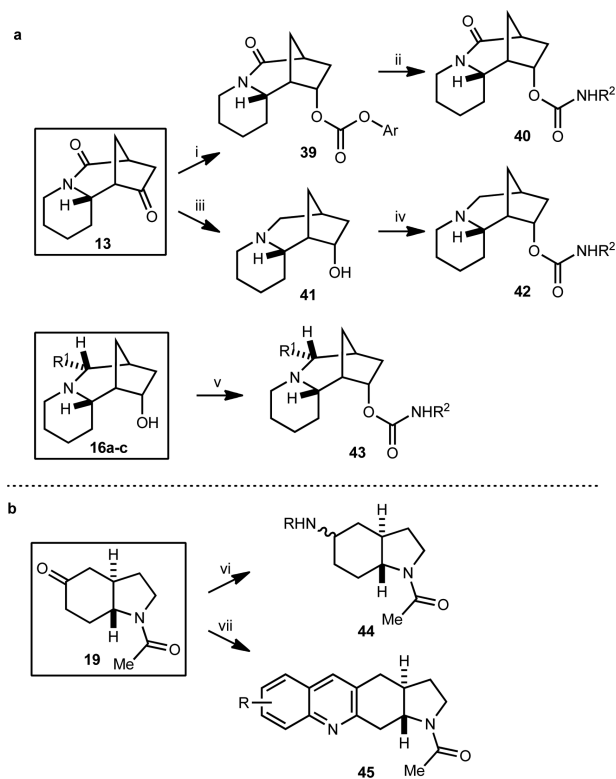
Figure 4. Library construction from sparteine and mesembrine-inspired scaffolds
(**a**) Library construction from sparteine-inspired scaffolds led to carbamates generated both from lactam **13** directly or by first converting it to the amine-containing scaffold **41**. Similar chemistry could be used on the additional alkyl-group-containing scaffolds **16a–c**. (**b**) Amide scaffold **19** was converted into amine and quinoline libraries. A total of 132 unique structures, each obtained in >90% purity (HPLC, UV detector at 214 nm) and >10 mg quantities were obtained. Scaffold (number of final products obtained): **13** (44), **16a-c** (52), **19** (36). (i) a) $NaBH_4$, MeOH, rt, 88%, >19:1 dr, (b) 4-nitrophenyl chloroformate, pyridine, THF, rt, 95%; (ii) R^2NH_2, DCE, rt; (iii) $LiAlH_4$, THF, reflux, 80%; (iv) $R^2N{=}C{=}O$, MeCN, microwave, 110 °C; (v) $R^2N{=}C{=}O$, THF, rt; (vi) RNH_2, AcOH, $Na(OAc)_3BH$, THF; (vii) 2-nitrobenzaldehyde, Fe^0, 0.1M HCl, EtOH, 85 °C; then **19**, KOH, 85 °C.
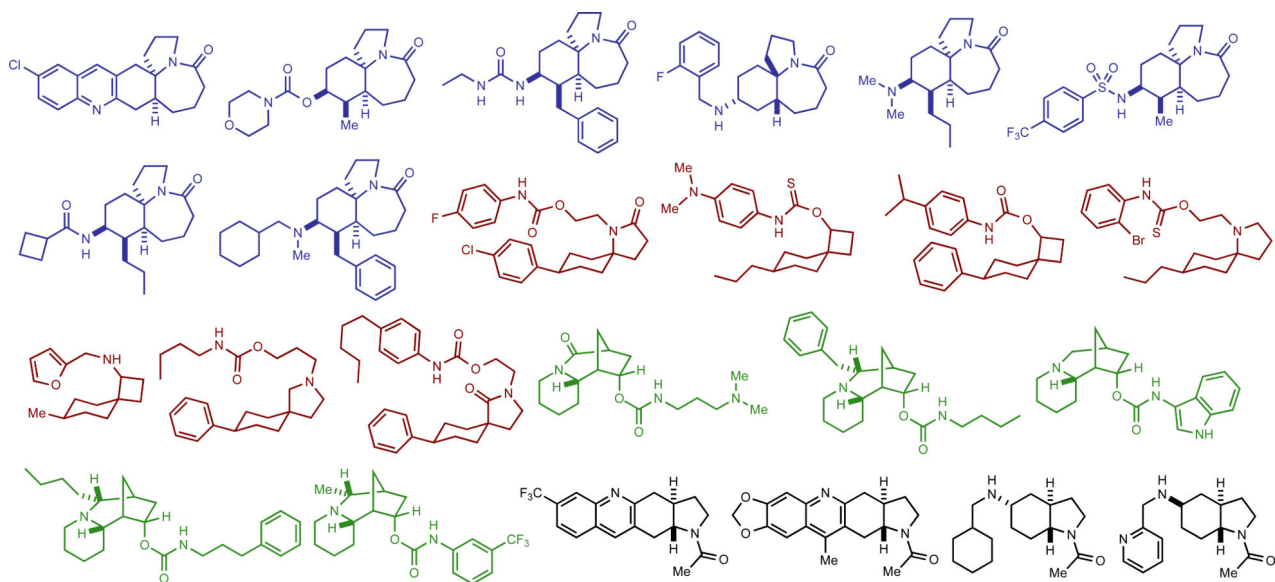
Figure 5. Representative selection of library compounds used in cheminformatic analyses.
For a full list of scaffold and library compounds used in this analysis, see **Supplementary Figs. 3 and 4**.
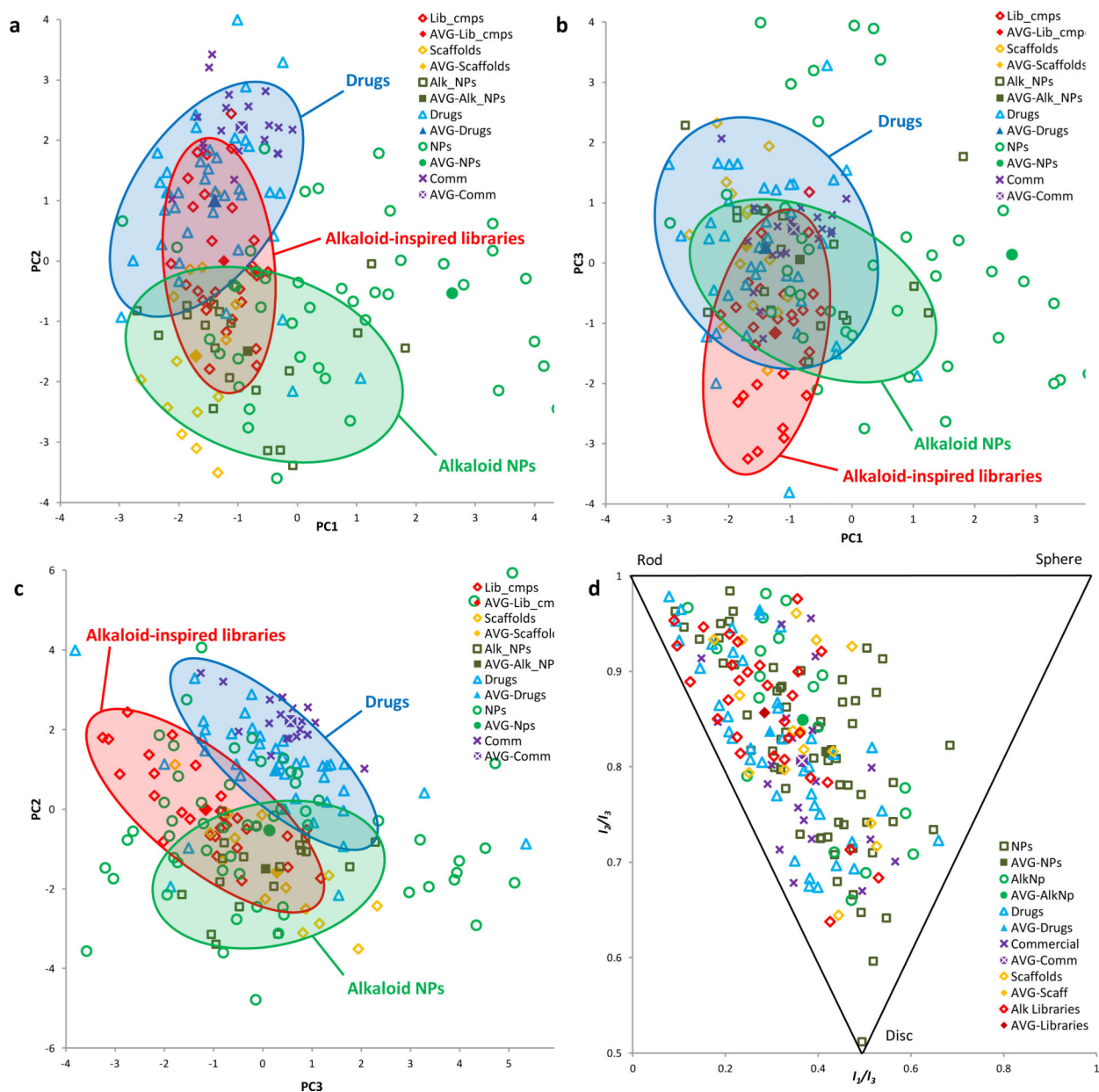
Figure 6. Cheminformatic analysis of alkaloid-inspired scaffolds and library members.
Structural and physiochemical properties of a representative selection of synthesized scaffolds (14 compounds, yellow diamonds) and library members (29 compounds, red diamonds) were compared with those of alkaloid NPs (20 compounds, green squares) and an established reference set[48] of drugs (40 compounds, blue triangles), commercially available drug-like molecules (20 compounds, purple crosses) and NPs (60 compounds, green circles) using principal component analysis (PCA) and principal moment of inertia (PMI) analysis. The hypothetical average (mean) structure for each series is also plotted (AVG-). (**a**) PCA plot of PC1 v PC2. (**b**) PCA plot of PC1 v PC3. (**c**) PCA plot of PC2 v PC3. (**d**) PMI plot showing the 3-dimensional shape of the lowest energy conformer of each compound. The

shaded red, green, and blue areas outline the regions of the plot where the majority of our alkaloid inspired libraries, alkaloid NPs, and drugs, respectively, are located.