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Review

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Progress and opportunities of pseudo-natural-product design in molecular discovery

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Dedicated to Prof. Léon Ghosez on the occasion of his 90th birthday

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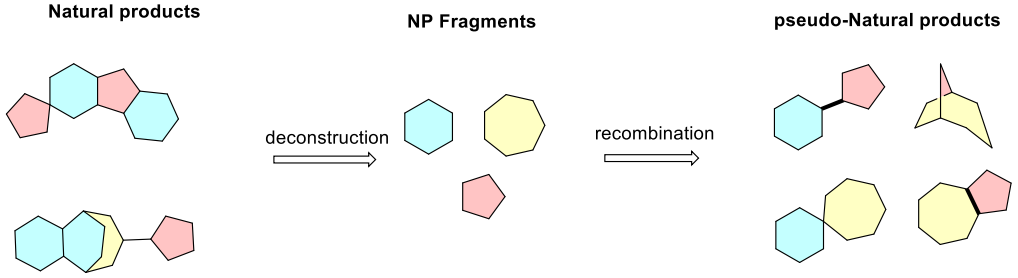
Abstract

Natural products have been a rich source of bioactive molecules. However, the natural evolution of natural products is a long process, which largely limits their further exploration of biologically-relevant chemical space. The pseudo-natural-products approach provides an efficient strategy to rapidly explore biologically-relevant chemical space, leading to the discovery of novel bioactive compounds. In general, pseudo-natural products are generated through the *de novo* recombination of natural-product fragments with different arrangements and connectivity patterns to afford new natural-product-like compounds that are unprecedented in nature. Herein, we describe the pseudo-natural-product concept and its design principles, highlight recent examples of pseudo-natural-product collections, and discuss potential future trends and opportunities of pseudo-natural-product design.



Keywords: Pseudo-natural products, design principle, natural-product fragments, diverse scaffolds

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1. Introduction

Natural products (NPs) are the result of nature's exploration of biologically-relevant chemical space through evolution, and their structures can, therefore, be considered biologically validated. NPs represent a rich source of bioactive compounds which have been successfully developed into biochemical tools and pharmaceuticals.[1] Nevertheless, natural evolution is a very slow process which has led to only a fraction of possible biologically-relevant NP-like space being explored by nature.[2] To overcome this evolutionary constraint, several NP-inspired, molecular-discovery-design principles have been developed, such as Complexity-to-Diversity, Biology-Oriented Synthesis, and Pseudo-Natural Products (PNPs).[3] The PNP concept combines the biological relevance of NPs with the rapid exploration of chemical space of fragment-based discovery (Figure 1).[4] By employing cheminformatics, NPs can be computationally deconstructed into NP fragments that retain the molecular properties of NPs.[5] Synthetic *de novo* recombination of these NP fragments into new arrangements can afford novel scaffolds that retain the biological relevance of NPs, but are not accessible by nature through existing biosynthetic pathways. PNP collections may explore new areas of biologically-relevant chemical space that may not be represented in either synthetic drug-like compounds or existing NP structures. Therefore, in combination with suitable screening technologies, the synthesis and biological evaluation of new PNP collections may lead to the discovery of compounds with unexpected or unprecedented bioactivities.

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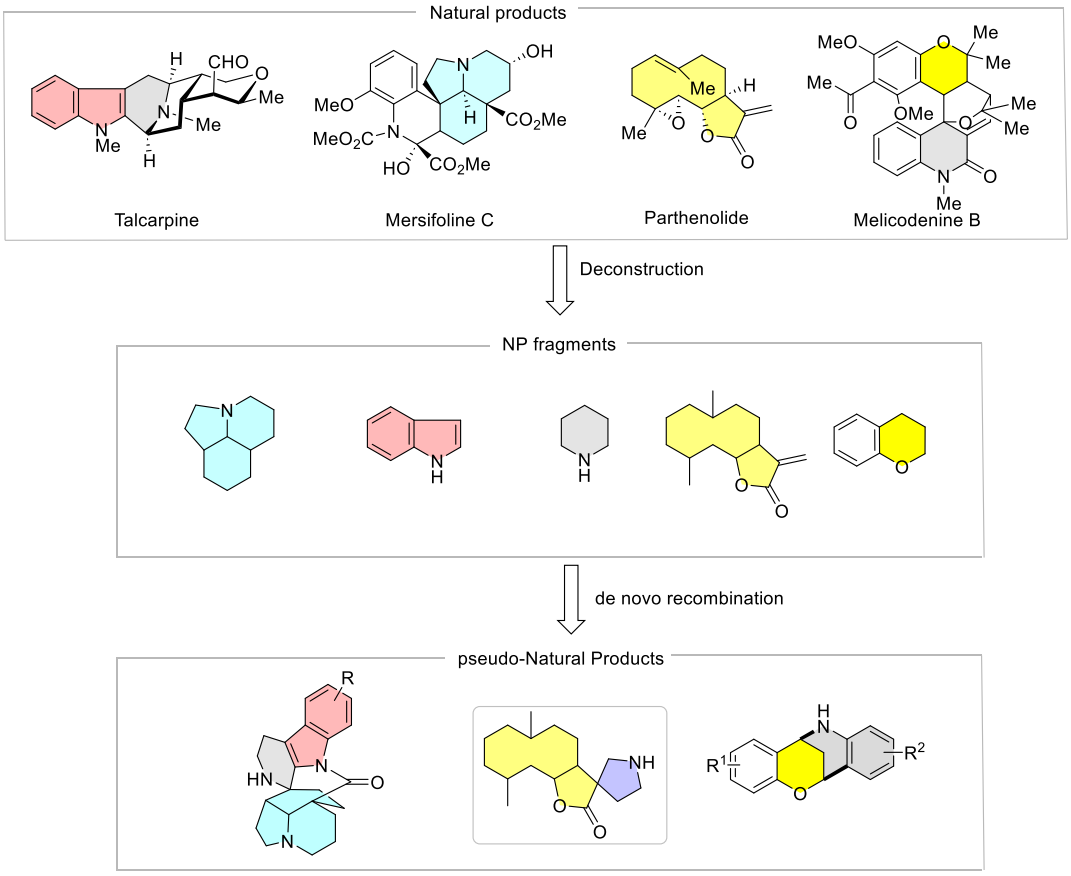

Figure 1. Overview of pseudo-natural-product design.

Since the PNP concept was first disclosed, several successful examples[6-8] and cheminformatic studies[9] have been reported to provide validation of the concept as a means to efficiently explore biologically-relevant chemical space. In this review, general PNP-design principles will be outlined, and recently reported PNP collections will be discussed with a focus on their design and synthesis. Additionally, current research trends and future opportunities for the PNP-design principle will be summarized.

2. Design Principle and Biological Evaluation of PNP Collections

In PNP design, NPs are first computationally deconstructed into NP fragments.[5] Either these NP fragments or NPs that are fragment-sized themselves, i.e., Alog P < 3.5, molecular weight 120–350 Da, ≤ 3 hydrogen-bond donors, ≤ 6 hydrogen-bond acceptors, and ≤ 6 rotatable bonds,[5] are then synthetically recombined to afford novel structures that do not occur in nature. Diversity in PNP collections can be obtained by 1) combining different NP fragments,[10] 2) combining similar fragments in different arrangements with different connectivity patterns, such as edge-fusion, bridged-fusion, and spiro-fusion, [11] and 3) exploring three-dimensional diversity by accessing different stereoisomers (Figure 2).[12]

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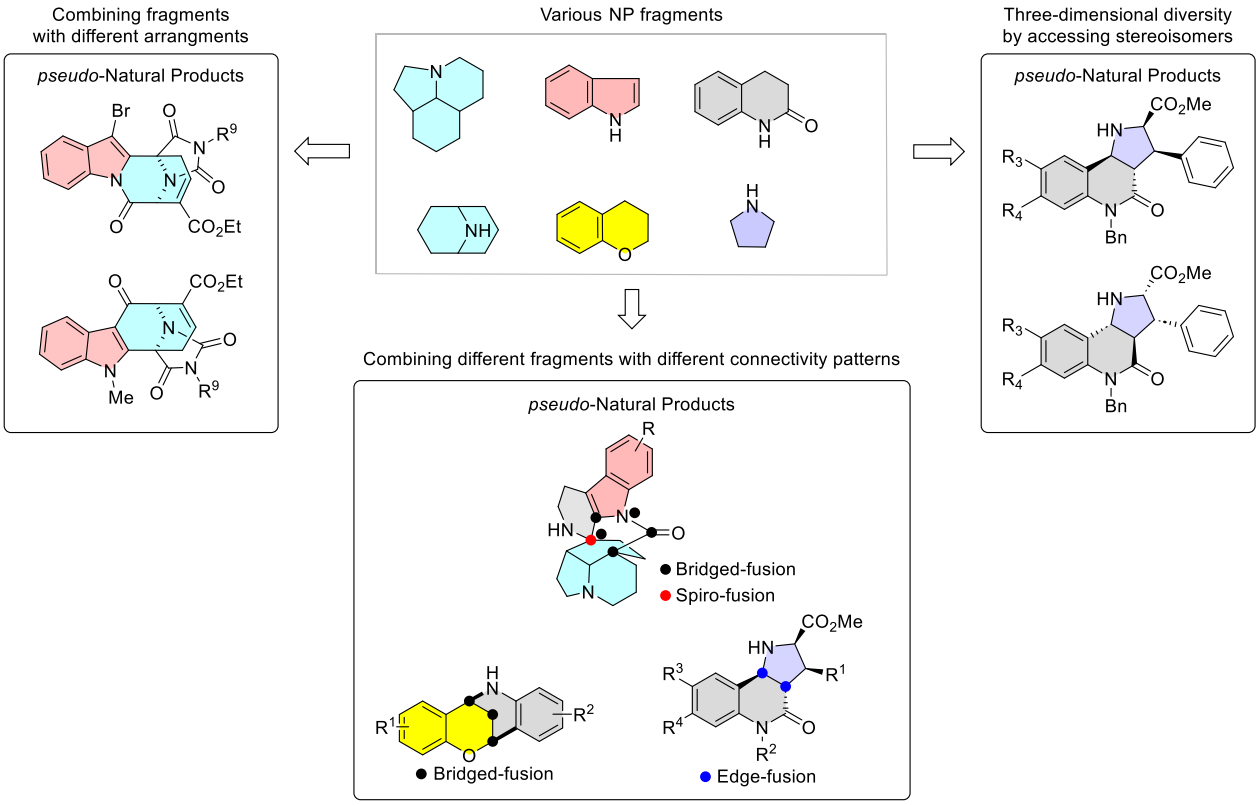

Figure 2. General design principle for diverse PNPs collections.

Since PNPs are new, their structures are not yet linked to bioactivities. Therefore, biologically broad, and unbiased screening technologies, such as phenotypic assays and morphological profiling, are best suited to uncover the bioactivities of PNP collections. In particular, the "Cell Painting Assay" (CPA)[13] has been a valuable tool for identifying and characterizing bioactive PNPs.[14] The CPA quantifies morphological changes of cells and cellular compartments upon compound treatment. Hundreds of features are extracted via fluorescence microscopy and are then combined to afford a profile that represents the morphological changes induced by the compound. These profiles can then be compared to reference compounds with annotated bioactivities to generate target or mode-of-action hypotheses.

3. Recent Examples of PNP Collections

3.1. Monoterpene indole alkaloid PNPs

Monoterpene indole alkaloid (MIA) NPs (Figure 3) are derived from strictosidine. They have diverse bioactivities and have found use as chemical probes and therapeutics. [15-17] However, the structures of existing MIA NPs are limited since they are all biosynthetically derived from a strictosidine intermediate. To overcome this limitation, Xie et al. employed synthetic chemistry to combine MIA NP fragments in arrangements that are not found in nature. [18] Intermolecular Pictet-Spengler reactions of ketone **1** and either tryptophol or tryptamine derivatives in acidic conditions combined a 6*H*-lilolidine fragment with either a 4*H*-pyranoindole or a 4*H*-β-carboline NP fragment with a spirocyclic fusion pattern to afford compounds **2**. The indole nitrogen and methyl ester of **2** were aligned properly for intramolecular lactamization which could be induced in the presence of triazabicyclodecene (TBD) to yield compounds **3** with a bridged fusion pattern. The MIA PNP collection was

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compared to MIA NPs via cheminformatic analysis and was found to occupy similar chemical space including high spatial complexity-density.[19] Biological evaluation of the MIA PNP collection via the CPA and subsequent validation assays led to the identification of novel inhibitors of DNA-synthesis and tubulin polymerization.

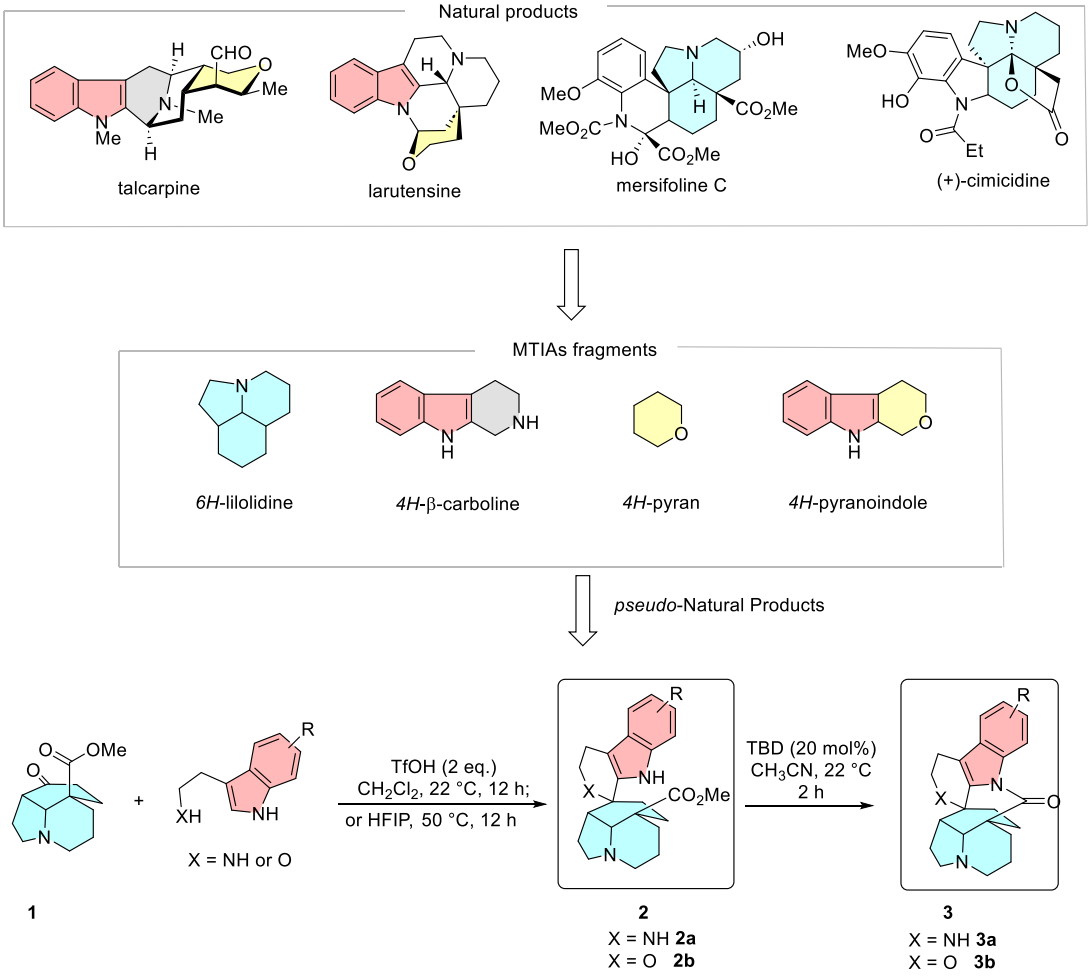

Figure 3. Design and synthesis of a MIA PNP collection.

3.2. Chromaline PNPs

The previously reported PNP classes of chromopynones, i.e., the combination of chromane and 4*H*-pyrimidinone, [4] and pyrrolidine-4H-quinolines, i.e., the combination of pyrrolidine and 4*H*-quinoline, [11] share a bridged connectivity pattern and were found to produce significantly different CPA profiles. This finding indicated that the rearrangement of these fragments with a conserved bridged fusion pattern may produce a new, morphologically-different compound class. With this in mind, Zinken et al. combined chromane and 4*H*-quinoline fragments via a bridged connectivity pattern. The core scaffold of these chromaline PNPs (Figure 4a) could be rapidly accessed through a four-step synthesis route with an acid-catalysed intramolecular cyclisation as the key step.[20] The synthesis sequence began with a Mannich-type reaction employing 2-hydroxyacetophenone and 2-nitrobenzaldehydes in the presence of aniline and I_2 to afford nitro-functionalized flavanones **4** (Figure 4b). The ketone and nitro groups of the flavanones **4** were reduced with $NaBH_4$, and subsequent Béchamp nitro reduction readily generated *cis*-isomers **5**. [21] An acid-mediated cyclisation was developed and applied to construct the core PNP scaffold **6** (Figure 4c), regardless of diastereomeric configuration. The compound collection was further expanded by functionalizing alcohols and amines via

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Mitsunobu and amide-coupling reactions, respectively, to afford a 39-member collection of chromaline PNPs. The chromalines were compared to chromopynones and pyrroquinoline classes via the CPA and were found to have morphological profiles significantly different from the guiding PNP classes. These results demonstrate that the CPA may be used as a tool to rationally design compound collections to explore new areas of biological space.

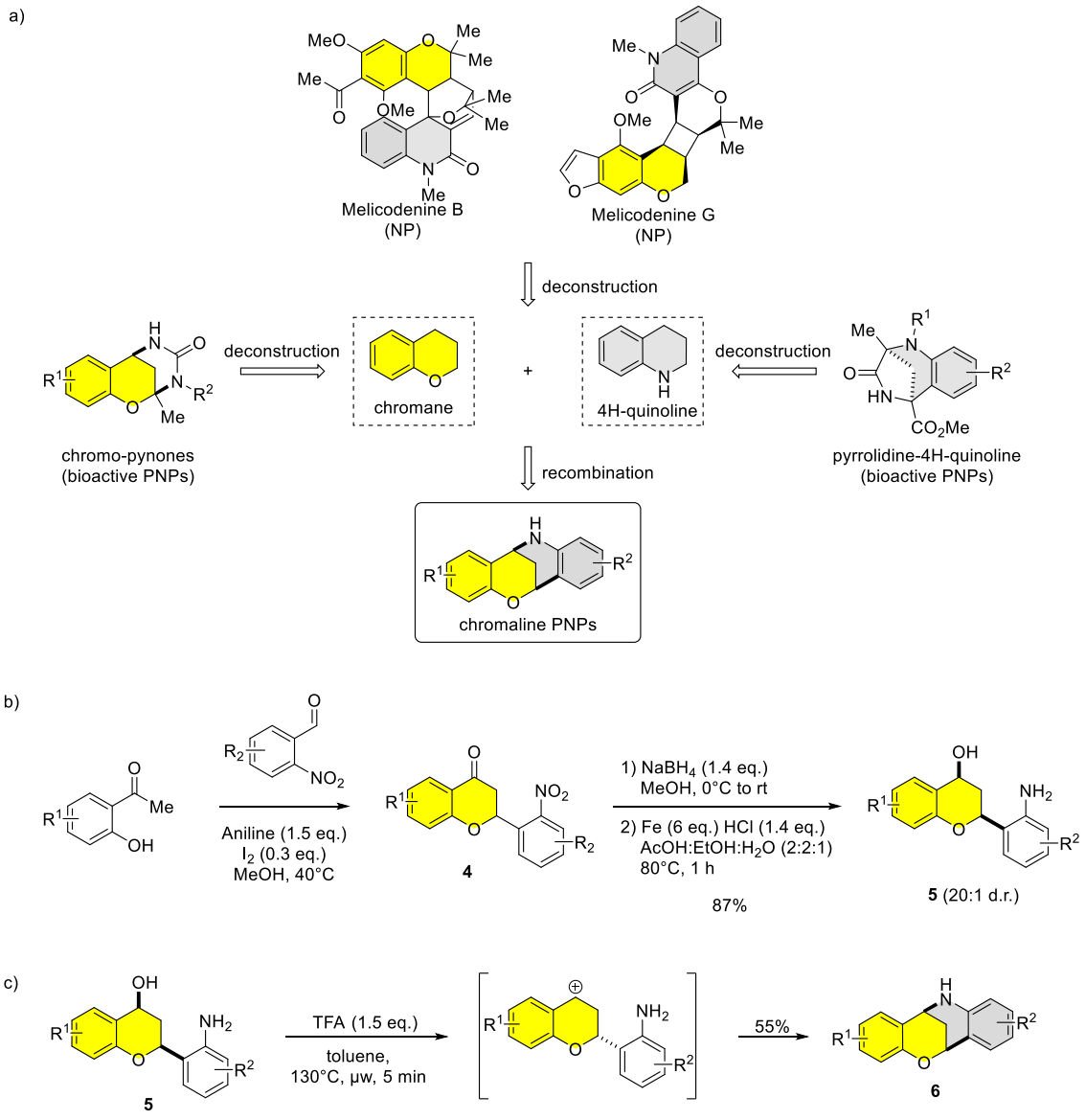

Figure 4. Design and synthesis route for chromaline PNPs.

3.3. Pyrrolo[3,2-c]quinoline PNPs

Pyrrolidine and tetrahydroquinoline are common fragments in biologically-active NPs. However, their combination with different arrangements and connectivities are rarely found in nature, and, therefore, a novel arrangement of these NP fragments may lead to access of new biologically-relevant chemical space. Liu et al. designed a class of pyrrolo[3,2-c]quinolines (Figure 5).[22] Rapid access to these compounds was possible through the development of a new enantioselective intramolecular 1,3-dipolar cycloaddition employing a AgOAc/(*S*)-DMBiphep catalyst to produce twenty-nine pyrrolo[3,2-c]quinolines **7** with excellent yields (up to 98%) and

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enantioselectivities (up to 99% *ee*). It is worth noting that the site-specific introduction of a substituent in 4*H*-quinoline has a pronounced effect on enantioselectivity; the substituent in the R^3 position especially led to higher enantioselectivity. Biological evaluation of the collection revealed a novel smoothened antagonist that potently inhibits the Hedgehog (Hh)-signalling pathway. Interestingly, the inhibition of Hh signalling is significantly influenced by the absolute configuration of the most potent compound, highlighting the importance of utilizing enantioselective catalysis for the synthesis of PNP collections.

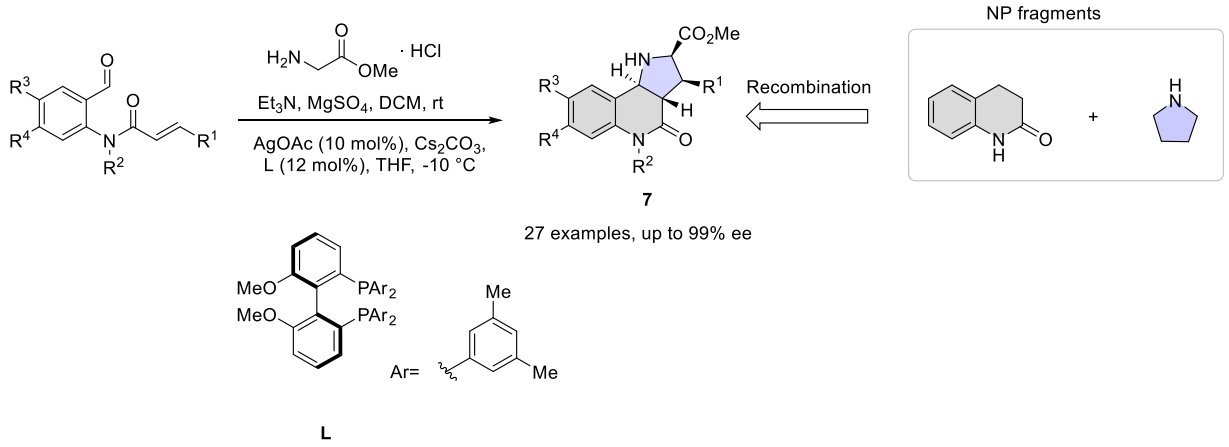

Figure 5. Asymmetric synthesis of pyrrolo[3,2-*c*]quinolines via intramolecular 1,3-dipolar cycloadditions.

3.4. Macroline- and sarpagine-inspired PNPs

The indolo[3.3.1]homotropane fragment is present in a number of compounds with diverse bioactivities, and is a core scaffold for some NPs such as macrolines and sarpagines. Inspired by these NPs, Aoyama et al. designed a collective synthesis of macroline- and sarpagine-inspired compounds by using both biology-oriented synthesis and PNP-design principles (Figure 6a). [23] Phosphine-catalyzed [4+2] cycloadditions employing ketimine derivatives **8**, and allenoates **9**, were used to afford 4*H*-pyridines **10** as single diastereomers. Additionally, the reaction could be carried out enantioselectively by employing a chiral phosphine catalyst. Compounds **10** were used as divergent intermediates. When subjected to TFA, **10** underwent intramolecular Friedel-Crafts-type C-acylations to construct the indolo[3.3.1]homotropane scaffold and could be functionalized to afford a small collection of BIOS (biology oriented synthetic) compounds **11**. Indolo[3.3.1]homotropanes **11** could be fused with a hydantoin fragment upon liberation of a free amine, reaction with an isocyanate, and amide-bond formation with the nearby methyl ester to afford PNPs **13**. From divergent intermediate **10**, a novel Sn-mediated intramolecular indole-*N*-cyclization was developed and employed to effectively fuse the [3.3.1]homotropane fragment to the indole with a different orientation to yield PNPs **12**. Interestingly, this reaction did not occur in the absence of Me_4Sn or in the absence of both $Pd(dppf)Cl_2$ and CuI. Additionally, the liberation of an amine from **12** and reaction with isocyanate derivatives led to the incorporation of a hydantoin fragment and the construction of PNPs **14**. A cheminformatic analysis of this PNP collection indicated that the synthesized compounds have similarities to both NPs and drugs. Morphological profiling via the CPA and subsequent validation assays led to the identification of one representative of **13** as a novel chemotype for microtubule modulation.

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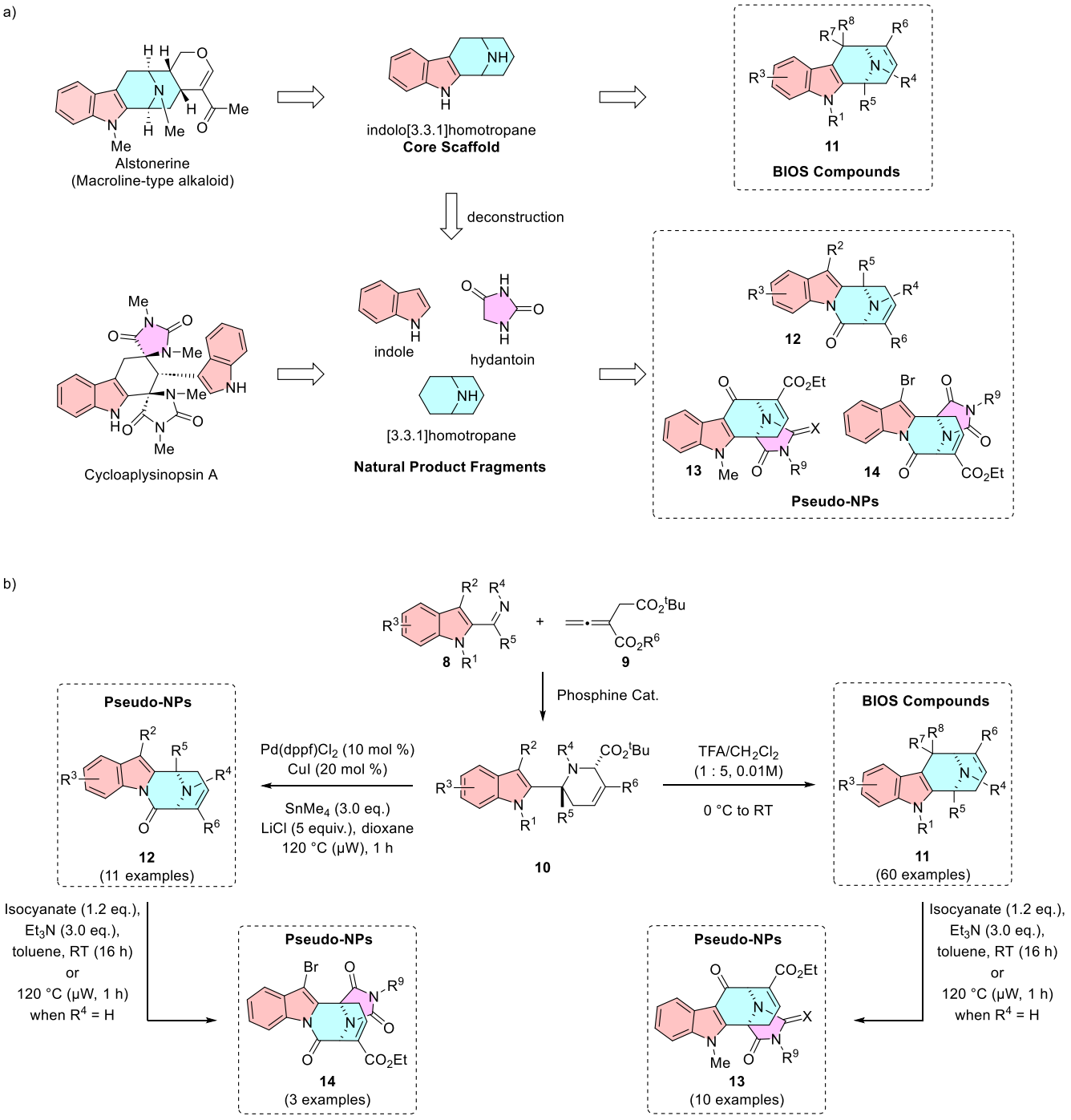

Figure 6. Design and synthesis of a biology-oriented synthesis- and PNP-inspired compound collection.

3.5. Sesquiterpenoid alkaloid PNPs via complexity to diversity strategy

Sesquiterpene lactones, many of which are fragment sized, are a class of bioactivity-rich NPs,[24-26] and, using them as an example, Liu et al. combined the PNP design principle with the complexity-to-diversity strategy. [12] Various sesquiterpene NPs were subjected to ring-distortion reactions to provide structurally diverse sesquiterpene-like fragments as building blocks. Biosynthetically-unrelated pyrrolidine moieties were subsequently fused to these fragments via 1,3-dipolar cycloaddition reactions to afford a collection of pseudo-sesquiterpenoid alkaloids (Figure 7a). A stereo-complementary synthetic approach was developed by employing different chiral ligands and conditions for cycloaddition reactions, ultimately resulting in a range of

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stereochemically-diverse pyrrolidine moieties (Figure 7b). When the ferrocene-derived ligand **L3** was employed, the resulting dipolar cycloaddition yielded compound **16** with excellent *endo-Si* selectivity. Opposite configuration of the pyrrolidine moiety could be achieved by employing *ent*-**L3** under the same conditions to afford **17**. Furthermore, using (*R*)-DTBM Segphos **L4** as a ligand in 1,2-dichloroethane generated compound **18** with almost quantitative *exo-Si* selectivity. More interestingly, the choice of solvent was shown to be crucial for controlling selectivity. In THF, the *endo-Re* attack was favored; however, the selectivity switched to *exo-Si* when chloroform was employed as the solvent (see compound **19**). Biological evaluation of this stereochemically- and structurally-diverse compound collection showed diverse biological performance. Furthermore, a novel inhibitor of Hh-dependent osteoblast differentiation was identified in this compound collection.

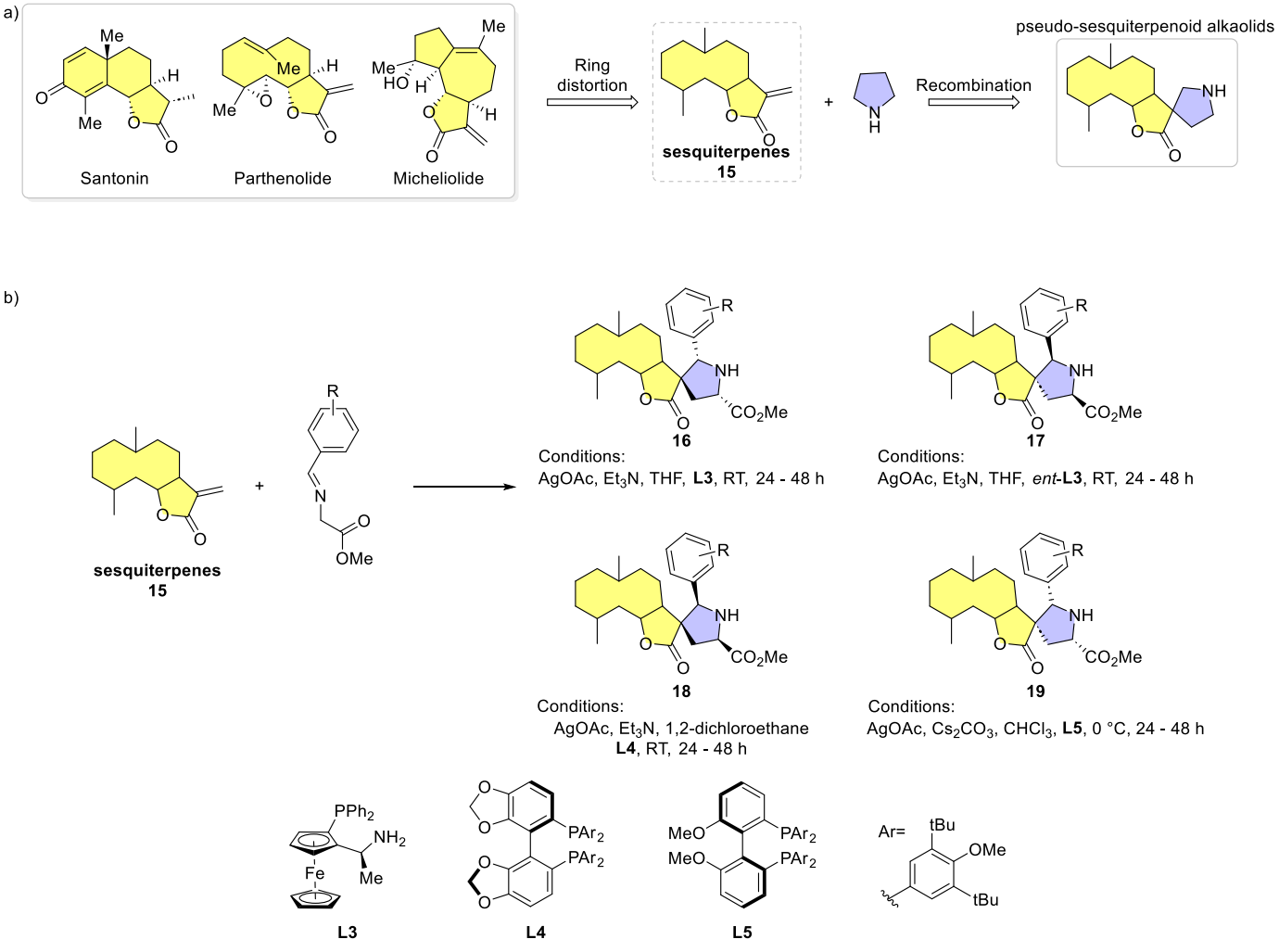

Figure 7. Combination of PNP design and complexity-to-diversity principles to afford diverse pseudo-sesquiterpenoid alkaloids**.**

3.6. Camptothecin-like PNPs

Camptothecin (CPT) is an alkaloid NP that exhibits anticancer properties via inhibition of topoisomerase I. Srikanth et al. used the PNP strategy in combination with the complexity-to-diversity strategy to design a new class of CPT-like compounds through the combination of the alkaloid fragment 4*H*-pyrroloquinolinone and the sugar moiety, furanose (Figure 8a). [27] To access this PNP collection, tryptamine derivatives and a furanose system **20** were employed as starting materials in Pictet–Spengler reactions in the presence of a TFA catalyst in

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dichloromethane at -78 °C to provide β-carboline intermediates **21** in good yields and with excellent diastereoselectivities (Figure 8b). Compounds **21** were treated with 4-dimethylaminopyridine (DMAP) in MeOH at 45 °C to induce the formation of intramolecular aza-Michael addition products **22**. The aza-Michael addition showed good compatibility with electron-donating or withdrawing substituents on the aromatic ring and afforded the desired products in moderate diastereoselectivities (7:3 dr) with *trans* isomers as the major products. To access the 4*H*-pyrroloquinolinone fragment, a ring-distortion strategy was developed to promote indole oxidative ring enlargement and subsequent ring formation. Thus, compounds **22** were treated with $NaIO_4$ in a solvent mixture of MeOH/THF/H_2O to generate the medium-sized-ring ketolactam intermediate **23**. Subsequently, intermediates **23** underwent transannular aldol condensations in the presence of Cs_2CO_3 in two steps to afford the final CPT-like PNPs **24** in moderate yields. The focus of this work was on the synthesis of the PNPs, and biological evaluation of the compounds was not reported.

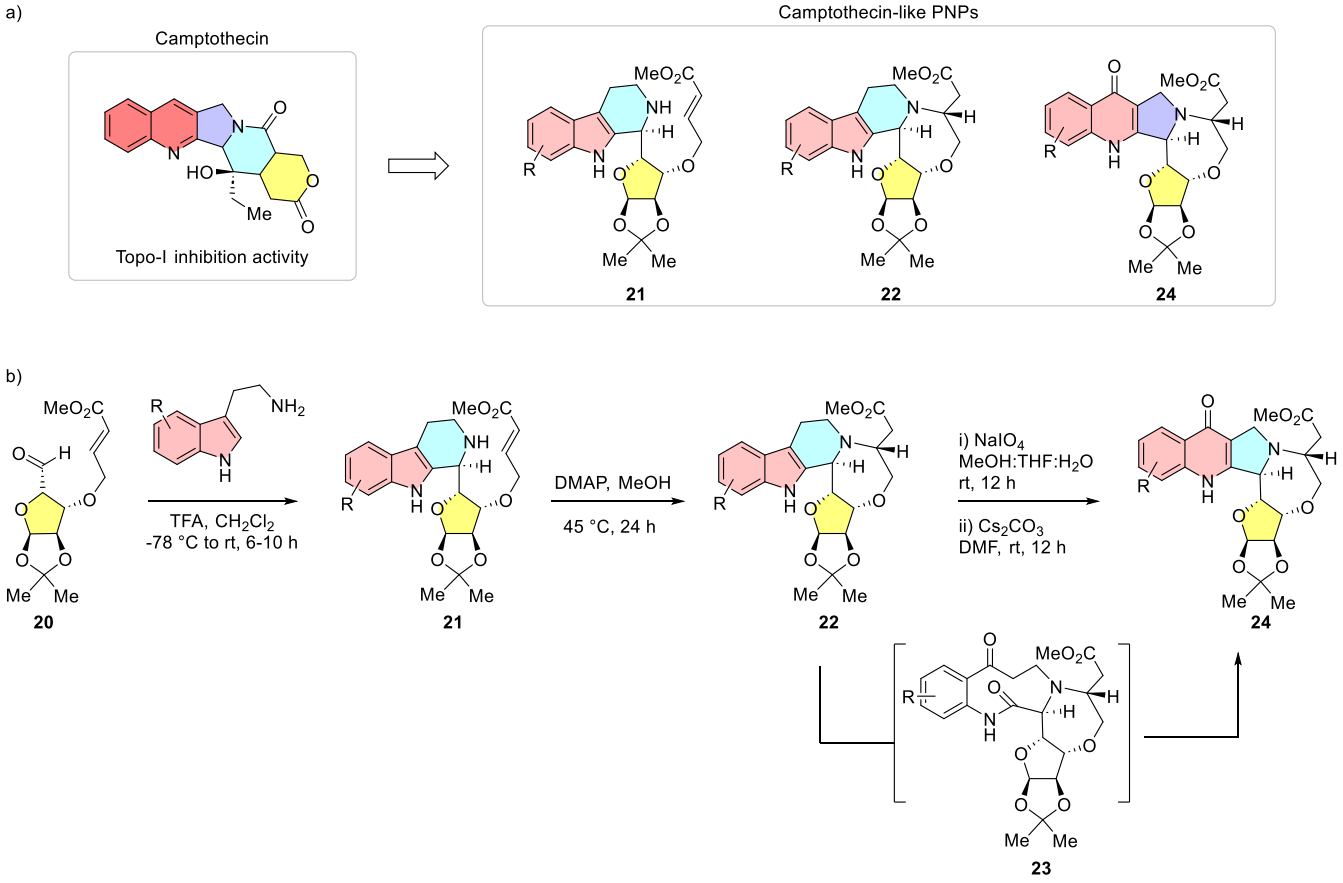

Figure 8. Diastereoselective synthesis of camptothecin PNPs.

3.7. Rutaecarpine-like PNPs

Rutaecarpine is a bioactive alkaloid that is isolated from the medicinal herb *Evodia rutaecarpa*, and has an abundance of bioactivities including vasodilatory, anti-platelet activation, anti-inflammatory, anti-oxidant, anti-fibrosis, and lipid-lowering activities (Figure 9a).[28-33] In order to more broadly explore the chemical and biological space of the rutaecarpine system, Qin et al. developed a synthetic route to access a novel rutaecarpine-derived PNP collection with *C*-seco skeletons (Figure 9b). [34] Aldehyde **25** reacted with *o*-phenylenediamine or *o*-aminobenzenethiol derivatives in the presence of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) to afford benzimidazoles **26** and benzothiazoles **27**, respectively. Additionally, **25** was reacted with o-aminobenzamides

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in the presence of tetrabutylammonium hydrogen sulfate (TBAST) to yield quinazolinones **28**. Esters **26-28** could be functionalized by amidation reactions to afford the pseudo-rutaecarpine collection (**29-31**). It is worth noting that, in some cases, the amidation of compound **27** required conditions developed by the Szostak group[35] to afford the desired products. Interestingly, this class of PNPs retains the anti-inflammatory activity of the guiding NP, and inhibits the activation of MAPK/NF-κB pathways with a good hepatoprotective effect.

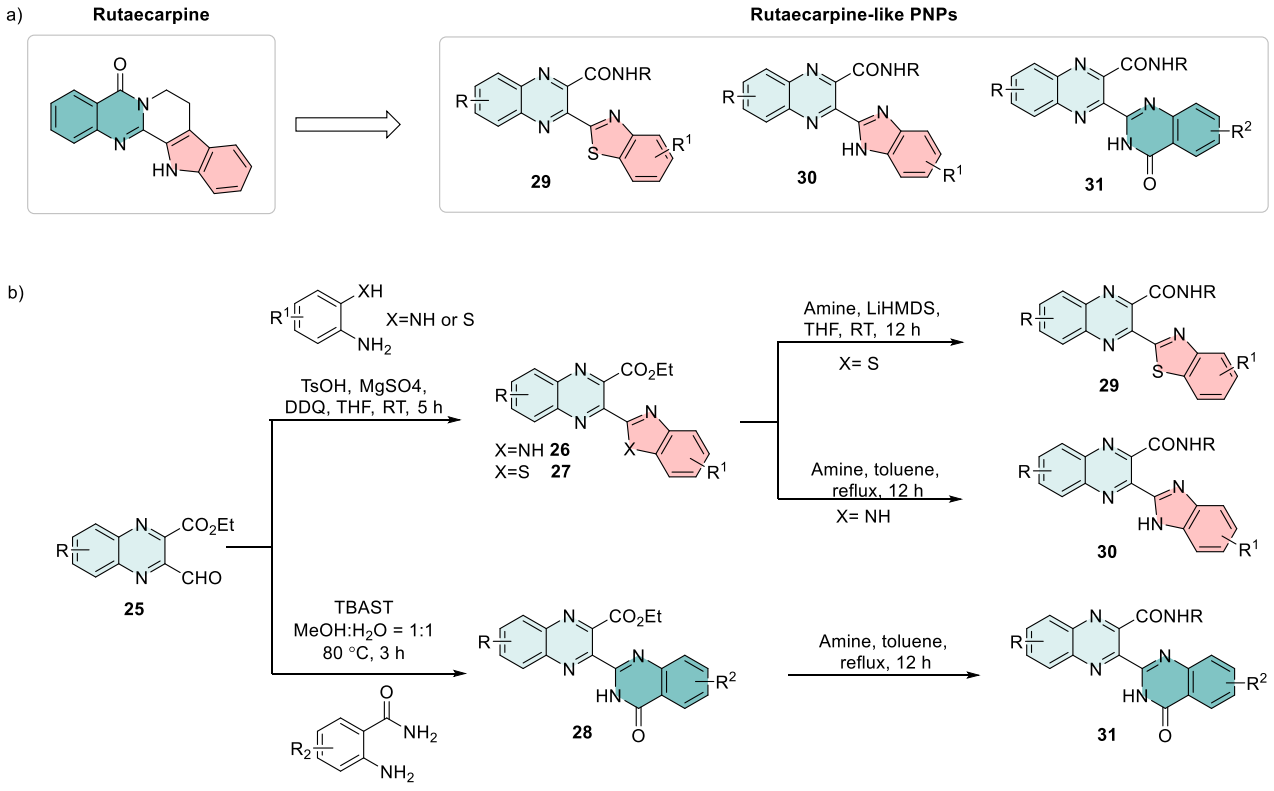

Figure 9. Design and synthesis of pseudo-rutaecarpines.

3.8. Indole-[3.3.1]homotropane PNPs

The azabicyclo[3.3.1]nonane fragment is found in several biologically-active alkaloid NPs, and can be difficult to construct due to its high strain energies. In 2022, Tan et al. developed a novel asymmetric cascade to construct *N*-bridged [3.3.1]-containing scaffolds that include indole fragments in orientations that are known to be produced in nature (Figure 10). [36] In this synthetic methodology, indole-based α,β-unsaturated ketones and cyclic azomethine ylides were employed as substrates with chiral phosphonium/thiourea catalyst (**32**) to induce asymmetric 1,3-dipolar cyclizations and afford intermediates **33** after 36 h. The ketone of these intermediates was subsequently activated with direct addition of BF_3•Et_2O to induce ring opening followed by an intramolecular Friedel–Crafts-type reaction between the indole and iminium moieties **34** to afford the desired azabicyclo[3.3.1]nonane compounds **35**. Several different substrates bearing various functional groups and substitution patterns were compatible with the developed procedure, resulting in the formation of the desired products in good yields, high enantioselectivities, and excellent diastereoselectivities. The diversity of the collection was expanded by functionalizing the ketone and ester moieties by reduction to result in a total collection of sixty-three (63) PNPs. Finally, preliminary bioactivity studies showed that these *N*-bridged [3.3.1] compounds may have anticancer potential.

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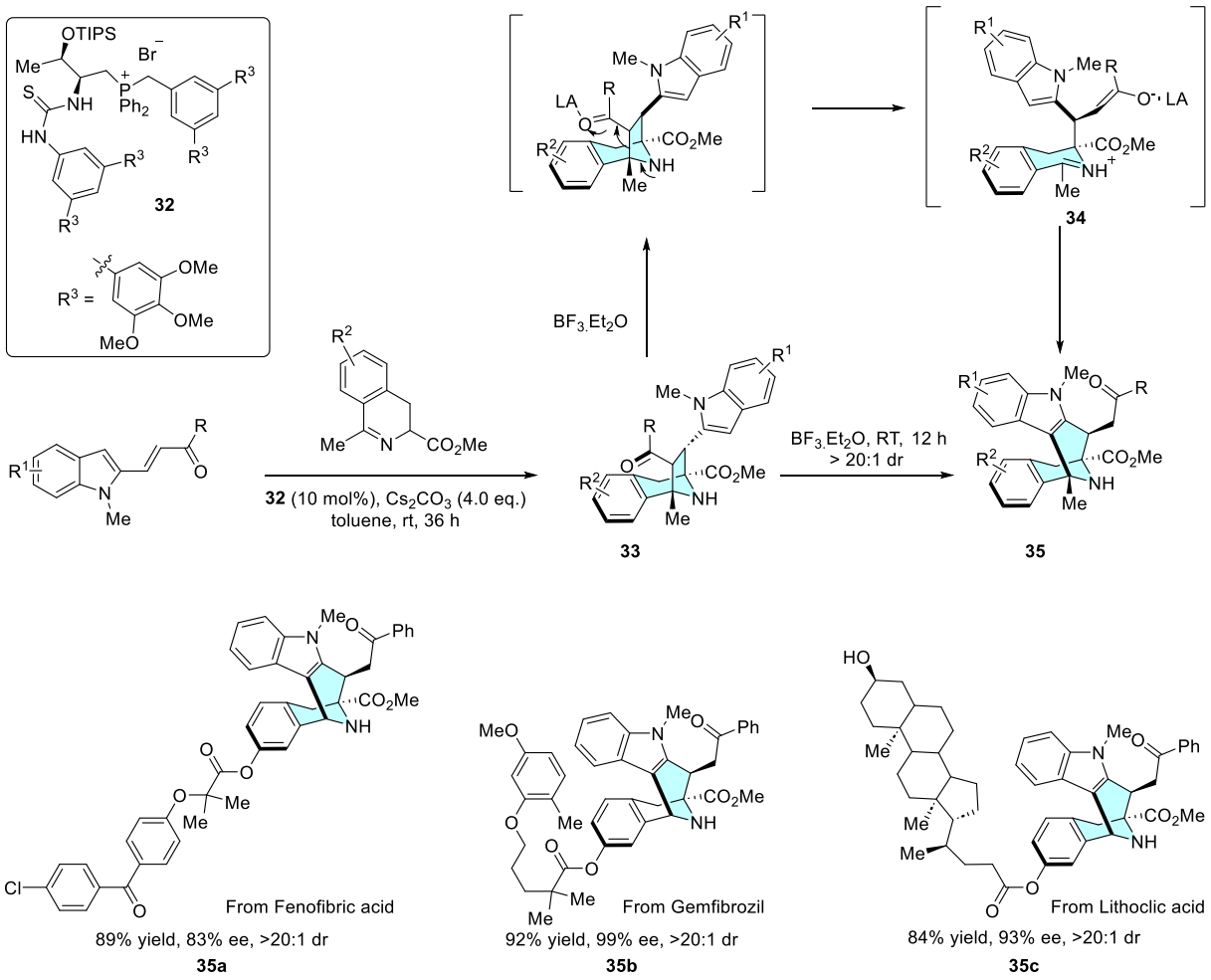

Figure 10. Asymmetric synthesis of *N*-bridged [3.3.1] ring systems by phosphonium salt/Lewis acid relay catalysis.

Conclusions

PNPs are the combination of NP fragments in arrangements not accessible in nature through known biosynthetic pathways. PNP design circumvents the evolutionary constraints placed on NPs, thereby, facilitating the exploration of biologically-relevant NP-like chemical space. The examples discussed above, and several other previously reported examples, showcase the PNP concept as a validated design principle for accessing novel biologically-active compound collections.

The design of novel PNP collections through the combination of different NP fragments in various arrangements and connectivities gives rise to a plethora of possible PNP scaffolds. Combining the logic of other molecular-design principles, such as biology-oriented synthesis,[23] and/or complexity-to-diversity,[12] with the PNP concept provides new opportunities to expand the chemical space occupied by a compound collection while retaining biological relevance. However, access to these structures may be synthetically challenging as the designed PNPs will likely retain the high complexity of NPs.[19] Therefore, the strategic implementation of existing synthetic methodologies, and the development of novel complexity-generating alternatives, will be crucial in facilitating the rapid construction of new PNP-compound classes with multi-bond-forming reactions that increase the fraction of sp^3-carbons, and overall stereogenic content in a stereoselective fashion that are

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particularly desirable. Linking the new PNP scaffolds to bioactivities will require the further development of broad and unbiased screening technologies and techniques to rapidly identify molecular targets.

The PNP concept may serve as a useful blueprint for the daunting task of exploring biologically relevant chemical space. Nevertheless, the importance of multidisciplinary collaboration required for the design, synthesis, and biological characterization of PNP collections should not be understated in the quest to discover new bioactive compounds that may be developed into chemical probes and/or therapeutics.

Acknowledgements

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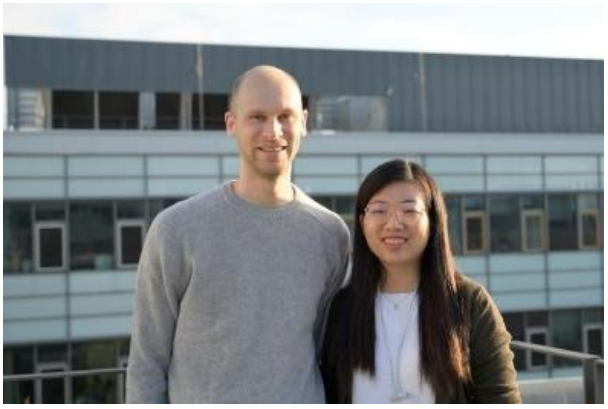
Authors' Biographies



Xiufen Cheng obtained her PhD degree under the supervision of Prof. Xisheng Wang at University of Science and Technology of China, where she worked on developing enantioselective C–H activations for synthesis of chiral heterocycles. From 2017, she joined Shandong Normal University as an assistant professor, during this time, she focused on quantitative chemoproteomic profiling of targets of small molecules. In 2021, she moved to the Max Planck Institute of Molecular Physiology in Germany as a postdoctoral fellow in the group of Prof. Waldmann where her current research focuses on rational chemical design of pseudo-natural products for the discovery of IDO1 protein chemotypes.

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