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A novel complexity-to-diversity strategy for the diversity-oriented synthesis of structurally diverse and complex macrocycles from quinine

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ABSTRACT

Recent years have witnessed a global decline in the productivity and advancement of the pharmaceutical industry. A major contributing factor to this is the downturn in drug discovery successes. This can be attributed to the lack of structural (particularly scaffold) diversity and structural complexity exhibited by current small molecule screening collections.

Macrocycles have been shown to exhibit a diverse range of biological properties, with over 100 natural product-derived examples currently marketed as FDA-approved drugs. Despite this, synthetic macrocycles are widely considered to be a poorly explored structural class within drug discovery, which can be attributed to their synthetic intractability.

Herein we describe a novel complexity-to-diversity strategy for the diversity-oriented synthesis of novel, structurally complex and diverse macrocyclic scaffolds from natural product starting materials. This approach exploits the inherent structural (including functional) and stereochemical complexity of natural products in order to rapidly generate diversity and complexity. Readily-accessible natural product-derived intermediates serve as structural templates which can be divergently functionalized with different building blocks to generate a diverse range of acyclic precursors. Subsequent macrocyclisation then furnishes compounds that are each based around a distinct molecular scaffold. Thus, high levels of library scaffold diversity can be rapidly achieved. In this proof-of-concept study, the natural product quinine was used as the foundation for library synthesis, and six novel structurally diverse, highly complex and functionalized macrocycles were generated.

1. Introduction

1.1. History

In the 1990 s, with the advent of high-throughput screening and combinatorial chemistry, the drug discovery industry moved towards the rapid and efficient synthesis of large collections of compounds.[1] It was hoped that by screening thousands (and even millions) of compounds, multiple novel therapeutic leads would be identified. Unfortunately, this expected surge in productivity did not materialise.[2] This disappointing degree of productivity has been primarily attributed to the relative lack of structural diversity within the libraries.

Typically, such libraries were comprised of flat, sp^2 rich and structurally similar compounds.[2–4] As a result, there has been a drive in recent years to develop robust methodologies that allow for the rapid generation of compounds possessing more complex and diverse sp^3-rich architectures.

1.2. Natural products

Natural products represent a highly diverse and structurally innovative compound class. They possess significant sp^3 character, chirality, diverse core scaffolds, differing ratios of hetero to non-hetero atoms and, computationally, occupy a larger fraction of chemical space than typical combinatorial libraries.[5–8] As such, natural products play a crucial role in the discovery of drugs.

Abbreviations: ADMET, adsorption distribution metabolism excretion and toxicity; CtD, complexity-to-diversity; DCC, *N,N′*-dicyclohexylcarbodiimide; DCE, 1,2-dichloroethane; DIPEA, *N,N′*-diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DMF, *N,N′*-dimethylformamide; DMSO, dimethyl sulfoxide; DOS, diversity-oriented synthesis; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimine; FDA, US food and drugs administrations; HATU, 1-[bis(dimethylamino) methylene]-1H-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate; HTS, high-throughput screening; NCE, new chemical entities; PMI, principal moments of inertia; PPI, protein-protein interaction; PTSA, *para*-toluene sulfonic acid; TEA, triethylamine; THF, tetrahydrofuran.

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Despite the number of new chemical entities (NCEs) having fallen in recent years, the number of natural product and natural product-derived NCEs has remained relatively high; they are responsible for approximately 33% of all small molecule drugs approved from 1981 to 2014.[5,9–17]

Despite their key role in drug development, natural products are underrepresented in compound screening collections. This is attributed to the challenges associated with their identification, isolation and synthesis. In recent years, a variety of strategies have been reported to tackle this issue and deliver libraries of natural product-like compounds, including utilisation of simplified core motifs, diverted total synthesis[18,19] and diversity-oriented synthesis (DOS).[5,7,20–28] However, whilst natural products and their derivatives have featured as the end-goal in many drug discovery programs (both DOS-focused and otherwise), their use as starting materials in the manufacture of compound libraries remains relatively rare. Recent years have witnessed a growing interest in the development of strategies for the synthesis of complex and diverse compounds from natural products.[29–31]

One such approach pioneered by Hergenrother and co-workers, is referred to as "complexity-to-diversity (CtD)"; this involves the production of complex natural product-like libraries via the controlled application of ring distortion reactions on readily available natural products.[12,21,30–36] The CtD approach, which was inspired by nature's proclivity to manufacture complex natural products from common intermediates, enables natural products which are already inherently structurally complex, to be rapidly converted into markedly different core scaffolds. The CtD strategy has been successfully applied to several readily available natural products, including gibberellic acid, adrenosterone, quinine, abietic acid and fumagillol.[21,30–32]

1.3. Macrocycles

Macrocycles (compounds containing a ring size of 12 atoms or more) have been shown to exhibit a diverse range of biological activities and feature in a variety of marketed drugs.[37–39] More specifically, natural-product derived macrocycles, of which over 100 are found as FDA-approved drugs, have demonstrated excellent efficacy as antibiotics and anticancer drugs.[40–45] They have been shown to exhibit good physiochemical and pharmacokinetic properties, binding with high affinity and selectivity to targets.[42,46]

Macrocycles possess unique structural properties that separate them from their acyclic small molecule counterparts and to which much of their useful biological activity is attributed. In particular, their potency is credited to their structural pre-organisation and ability to interact with multiple binding sites across a large area.[46] In addition, acyclic compounds suffer major entropic loss upon binding to proteins due to the restriction of their conformational degrees-of-freedom. This effect is less prominent during macrocycle binding, due to a higher level of pre-organisation.[44,47–49] Even with a restricted number of conformations, macrocycles still possess sufficient flexibility to allow them to mould to a protein surface.[42,50] As such, they represent excellent synthetic targets and show great potential in succeeding where small molecules have previously failed, especially in the modulation of PPIs.[51,52]

Their lack of compliance with Lipinski's "rule of five" bears some of the responsibility for the slow uptake of macrocycles in medicinal chemistry and HTS campaigns.[44] Furthermore their perceived synthetic intractability alongside a lack of understanding of their ADMET properties has led to concern over their suitability as pharmaceutical leads.[50] Despite the advantages illustrated above, macrocyclic compounds are severely under-represented and under-exploited within the drug discovery industry.[42] As of 2008, almost half of all new small molecule drugs are generated synthetically whilst almost all of their macrocyclic counterparts are derived from natural products with minimal decoration to their structures.[46] As such, there is an unmet need for a robust methodology for the production of structurally diverse macrocycles.

1.4. Summary

Herein, we report the development of a novel complexity-to-diversity (CtD) approach for the synthesis of libraries of novel, structurally complex and diverse macrocyclic scaffolds from natural product starting materials (Scheme 1). This approach exploits the inherent structural and stereochemical complexity in natural products in order to rapidly generate diversity and complexity through the use of simple chemistry. In this proof-of-concept study, the natural product quinine was used as the foundation for the library synthesis and six novel, structurally diverse, highly complex and functionalised macrocycles were generated.

2. Results and discussion

2.1. Aims

We considered that the natural product starting materials to be used in the CtD strategy should ideally be inexpensive, readily available, structurally interesting and feature a selection of chemically distinct functional groups that would act as handles for diversification. Based upon these criteria, we selected the alkaloid quinine for initial proof-of-concept studies. Furthermore, its historical use as an antimalarial drug suggests that its inherent complexity is sufficient to achieve biological selectivity, and with its two discrete quinoline and quinuclidine cage ring systems, quinine possesses excellent structural complexity.

2.2. Strategy

Of the variety of known synthetic transformations of quinine,[30,53–60] we identified two key conversions that would help in demonstrating our strategy.

Firstly, work carried out by Huigens III et al.[30] demonstrated the successful Hoffmann degradation of quinine into quinotoxine – a promising transformation for this project. Not only would it yield a much more synthetically amenable secondary amine, but it would furnish another structural template for macrocycle construction.[30] Secondly, work by Zhang et al.[55] illustrated a successful thio-ene reaction upon quinine, allowing a facile means for functionalisation of the pendant alkene.[55]

Construction of these two additional core templates began with the boiling of quinine (**1**) in an aqueous acetic acid solution, which promoted acid-catalysed degradation to afford quinotoxine **2**. To form the final core scaffold, quinine (**1**) was heated overnight at 80 °C in neat mercaptoethanol to deliver diol **3** (Scheme 2).

With these three core templates in hand, we anticipated that we could construct three different structural types of macrocycle (Scheme 3a). It was hoped that the first class of macrocycles (Mac1) could be constructed by esterifying general building blocks **4** to the pendant hydroxyl of quinine (**1**) to afford linear precursors of the form **5**. Subsequent treatment with Grubbs' II catalyst would then initiate ring-closing metathesis to yield scaffolds of the form Mac1.

Starting in a similar manner, the second class of macrocycles (Mac2) would begin with the chemoselective esterification of building blocks **6** to diol **3**, followed by the coupling of building blocks **8** to the secondary alcohol to generate linear precursors **9** (Scheme 3b). These azido-alkyne intermediates would then undergo copper-mediated click-type 1,3-dipolar cycloadditions to afford macrocyclic scaffolds of the form Mac2.