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An expedient strategy for the diversity-oriented synthesis of macrocyclic compounds with natural product-like characteristics

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ABSTRACT

Naturally-derived macrocyclic compounds are associated with a diverse range of biological activities, including antibacterial effects, and there are over 100 marketed macrocycle drugs derived from natural products. However, synthetic macrocycles are widely considered to be poorly explored in antibiotic development (indeed, within drug discovery in general). This has been attributed to challenges associated with the generation of such compounds. Whilst there are synthetic methods that can produce large collections of structurally similar macrocycles (i.e., compounds with varying appendages based around similar core macrocyclic ring architectures) there is a relative dearth of strategies for the efficient generation of more structurally diverse macrocycle collections in which there is greater variation in the nature of macrocyclic scaffolds present. Such macrocycle collections should contain compounds with a broad range of biological activities (including antibacterial activities) and the requisite robust synthetic methodology useful for analogue synthesis and lead optimization once an active compound has been identified in a biological screen. Herein, we describe a new and expedient diversity-oriented synthesis (DOS) strategy for the generation of a library of novel structurally diverse macrocyclic compounds with a high level of scaffold diversity. The strategy is concise, proceeds from readily-available starting materials, is modular in nature and features a variety of macrocyclisation techniques. In this proof-of-concept study, the synthesis of several previously unreported macrocyclic compounds was achieved. Each of these macrocycles was based around a distinct molecular scaffold and contained natural product-like structural features (e.g., three-dimensionality and multiple hydrogen bond donors and acceptors) as well as synthetic handles for potential further elaboration. The successful generation of these macrocycles demonstrates the feasibility of the new DOS strategy as a synthetic platform for library generation.

1. Introduction

The inexorable rise in antibiotic-resistant bacteria has led to a steady decline in the efficacy of existing therapies for the treatment of bacterial infections.[1,2] Moreover, the pace at which new antibacterial agents are being generated has decreased dramatically in recent decades, a legacy of insufficient investment in fundamental antibacterial research by pharmaceutical companies since the 1960s.[1,2] Consequently, humanity is facing the very real and disturbing possibility of a future without an effective method for the treatment of some common bacterial infections.[1,2] Thus, there is a clear and critical medical need for the discovery of novel antibiotics.[1,3]

Lead compounds for antibacterial chemotherapy can be obtained from two sources: nature (natural products) or de novo chemical synthesis.[1] Historically, nature has been by far the more important; most of the major classes of antibiotics in therapeutic use are natural products or semi-synthetic derivatives thereof.[1,3] Among these, a macrocyclic scaffold (a ring system of 12 or more atoms) is common (Fig. 1). Indeed, naturally-derived macrocycles constitute a large class of compounds with useful antibacterial properties.[4–6] Natural macrocyclic derivatives are also associated with a broad range of other attractive biological effects (including anticancer, antifungal and immunosuppressive activities)[5,7] and there are more than 100 marketed macrocyle drugs derived from natural products.[8] The diverse and interesting biological activities associated with the macrocyclic compound class has been attributed to characteristic structural features.[7,8] Their cyclic structure means that they have less conformational freedom than an equivalent acylic compound and so suffer a smaller entropic loss upon

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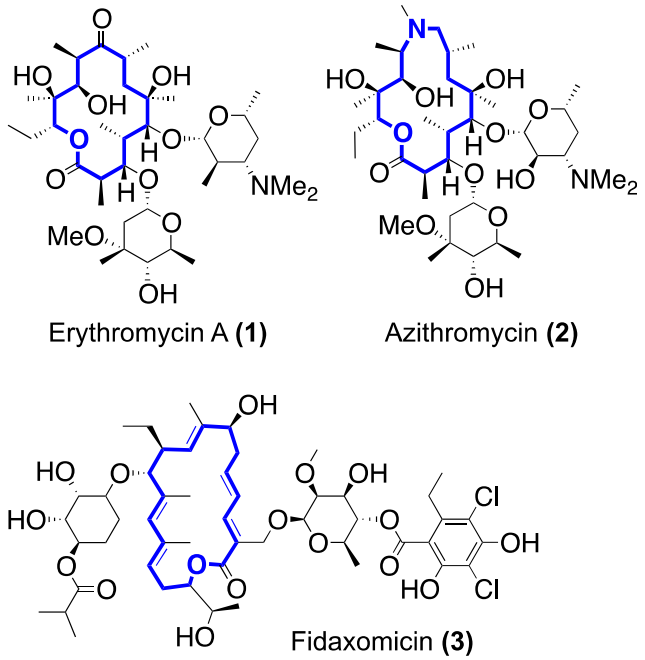

Fig. 1. Some examples of naturally-derived antibiotics which are based around macrocyclic scaffolds (highlighted in bold). Erythromycin A **(1)** and Fidaxomicin **(3)** are natural products and Azithromycin **(2)** is a semi-synthetic compound.[5]

binding to a biological target.[7–9] However, unlike smaller cyclic systems, macrocycles retain a certain flexibility, allowing them to potentially mould to a target surface in order to maximize binding interactions.[7–9] In addition, macrocycles can potentially adopt conformations in which polar motifs are buried away, leading to improved membrane permeability relative to their linear analogues.[7]

Clearly, macrocycles represent attractive targets in the search for new lead compounds for antibiotic development (indeed, drug development in general).[4,7,8] However, naturally occurring macrocycles are often highly complex in structure, which hampers their synthetic modification and pharmacokinetic optimization.[4,7,10] Thus, attention has shifted in recent years towards the exploration of synthetic macrocycles of medium complexity in drug discovery.[7,10] There has been notable success in this field, with many biologically active synthetic macrocycles with appropriate pharmacokinetic profiles identified[10] (including antibacterial lead compounds[11,12]). However, despite these encouraging examples, synthetic macrocycles are still widely considered to be relatively underexplored within drug discovery in general.[7–10,13] This has been attributed to challenges associated with the synthesis of such compounds, particularly in the context of the formation of the macrocyclic ring architecture.[7,9] Where present in a small molecule, the macrocyclic ring is generally considered to serve as the molecular scaffold (i.e., the core rigidifying structural feature of a molecule).[14] Whilst there are synthetic methods that can produce large collections of structurally similar macrocycles (i.e., compounds with varying appendages based around similar core macrocyclic scaffolds) there is a relative dearth of strategies for the efficient generation of more structurally diverse macrocycle collections in which there is greater variation in the nature of macrocyclic scaffolds present.[10,14] This is a crucial issue in the context of biological screening, since the overall structural, and thus functional diversity of a compound set (i.e., the range of biological activities displayed by the compounds) is known to be highly dependent upon the variety of molecular scaffolds present (the scaffold diversity) of the collection.[15–17] Macrocyclic collections with higher levels of scaffold diversity would be expected to provide a higher hit rate against a broader range of targets than libraries with lower scaffold, and thus overall structural, diversity.[14,15] Scaffold diverse macrocycle collections would therefore be expected to be particularly valuable in biological screens where the nature of the biological target is unknown (e.g., in phenotypic screening).[15,18] In addition, efficient access to structurally diverse macrocycles necessitates the development of synthetic methodology which is robust and broadly applicable in nature, which should facilitate the lead optimization process once a hit compound has been identified.[11,19]

Diversity-oriented synthesis (DOS) is a field of organic chemistry directed towards the efficient generation of molecular libraries that incorporate high degrees of structural diversity, including scaffold diversity.[15,20–22] The screening of DOS libraries has led to the identification of numerous novel biologically active small molecules, including several with antibacterial activities.[3,15,23–28] Recent years have seen the development of several DOS-type strategies specifically targeted at macrocyclic structures including examples from our own research group.[9,10,14,19,27,29–33] However, there remains considerable scope for further developments in the field. From a synthesis perspective, there are improvements that can be made in terms of the expediency of library construction and the efficiency in which scaffold diversity is generated.[19] In addition, large areas of macrocyclic chemical space, that may contain molecules with exciting biological properties (e.g., critically needed new antibacterials), still remain under-explored. These considerations highlight the need for new and expedient DOS strategies towards previously undescribed macrocyclic compounds. Herein, we describe work towards the development of one such strategy, which is based around the use of readily-accessible phenolic carbonyls as key starting materials. In a proof-of-concept study the synthesis of several structurally diverse and previously unreported macrocyclic scaffolds was achieved, which provides a validation of this DOS strategy as a synthetic platform for library generation.

2. Results and discussion

2.1. Outline of the synthetic strategy

Many DOS pathways are based around a three-phase build/couple/pair (B/C/P) algorithm.[20] In the *build* phase, starting materials (or building blocks) are synthesized. These are then combined (coupled together) in the *couple* phase to yield densely functionalized substrates for the subsequent *pair* phase, which involves intramolecular reactions that join pairwise combinations of functional groups to generate distinct molecular scaffolds.[14,20] In recent years, the use of iterative *couple* steps (i.e., B/C/C/P, B/C/C/C/P, etc.) has been exploited as a means to increase the diversity of scaffolds accessible from a given set of building blocks.[14,34] For example, we have recently reported a DOS strategy towards macrocyclic peptidomimetic scaffolds that incorporates iterative *couple* steps.[14] It was thought that the iterative *couple* concept could be used as the basis for a new and expedient DOS strategy towards novel and diverse macrocyclic compounds. We conceived the use of readily-accessible phenolic compounds of the general form **4**, which bear an electrophilic carbonyl group and a nucleophilic hydroxyl group, as key starting materials (Scheme 1). It was hoped that each given aromatic compound would serve as a 'platform' onto which different building blocks (generated in the *build* phase of the DOS) could be attached through functionalisation of these two reactive sites (*couple* stages). This would then afford a range of distinct acyclic precursors, which could then undergo intramolecular reactions to furnish different macrocyclic compounds, each based around a distinct molecular scaffold (*pair* phases). More specifically, we envisaged the use of four general types of building blocks: the

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