ELSEVIER

Wanted: new multicomponent reactions for generating libraries of polycyclic natural products

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The amalgamation of two of combinatorial chemistry's most attractive concepts — natural product libraries and multicomponent reactions (MCRs) — should provide a powerful tactic for generating libraries of bioactive compounds. Yet, despite many recent advances in this area, only a few MCRs can deliver functionalized products whose structures closely resemble that of complex polycyclic natural products. A large proportion of recently developed MCRs are based on [4+2] or [3+2] cycloadditions, and isocyanide-based processes. Because of substrate limitations, however, they are not always ideally suitable for applications in diversity-oriented synthesis of natural product-like compounds. A promising area awaiting further development is the use of transition metal-catalyzed cascade reactions.

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Introduction

Natural products play a dominant role in the development of human therapeutics [1]. It is therefore not surprising that the importance of natural products as lead structures for the generation of combinatorial libraries has been highly emphasized in recent years. Several reviews have been written on this topic [2,3••], including excellent contributions from this journal [4,5•]. Likewise, the power of multicomponent reactions (MCRs) as highly convergent diversity-generating processes has been widely recognized, and the extensive global efforts of numerous laboratories have been reviewed frequently [6–9,10•,11•]. It seems only logical that the successful amalgamation of these two concepts — natural product libraries and multicomponent reactions — would deliver a most effective tactic for generating promising bioactive compounds. Although several reports have described the use of MCRs in the generation of libraries of functionalized heterocycles, there are relatively few examples of MCRs that generate the type of polycycles with multiple stereocenters often found in nature. In this context, the ideal MCR would possess the following attributes: (1) generate a polycyclic scaffold with a structure closely resembling that of a bioactive class of natural products; (2) be operationally simple and atom-economical, with applicability in both solution- and solid-phase library generation; (3) use simple substrates that are all readily available in a highly diverse array; (4) offer additional opportunities for post-MCR modifications of the reaction products.

This review describes a selection of recent examples of MCRs that afford close structural relatives of polycyclic bioactive natural products. The potential of these MCRs in diversity-oriented synthesis (DOS) [12] of natural product-like libraries is discussed with respect to the aforementioned criteria. The chosen examples of MCRs are divided into mechanistic classes.

Isocyanide-based MCRs

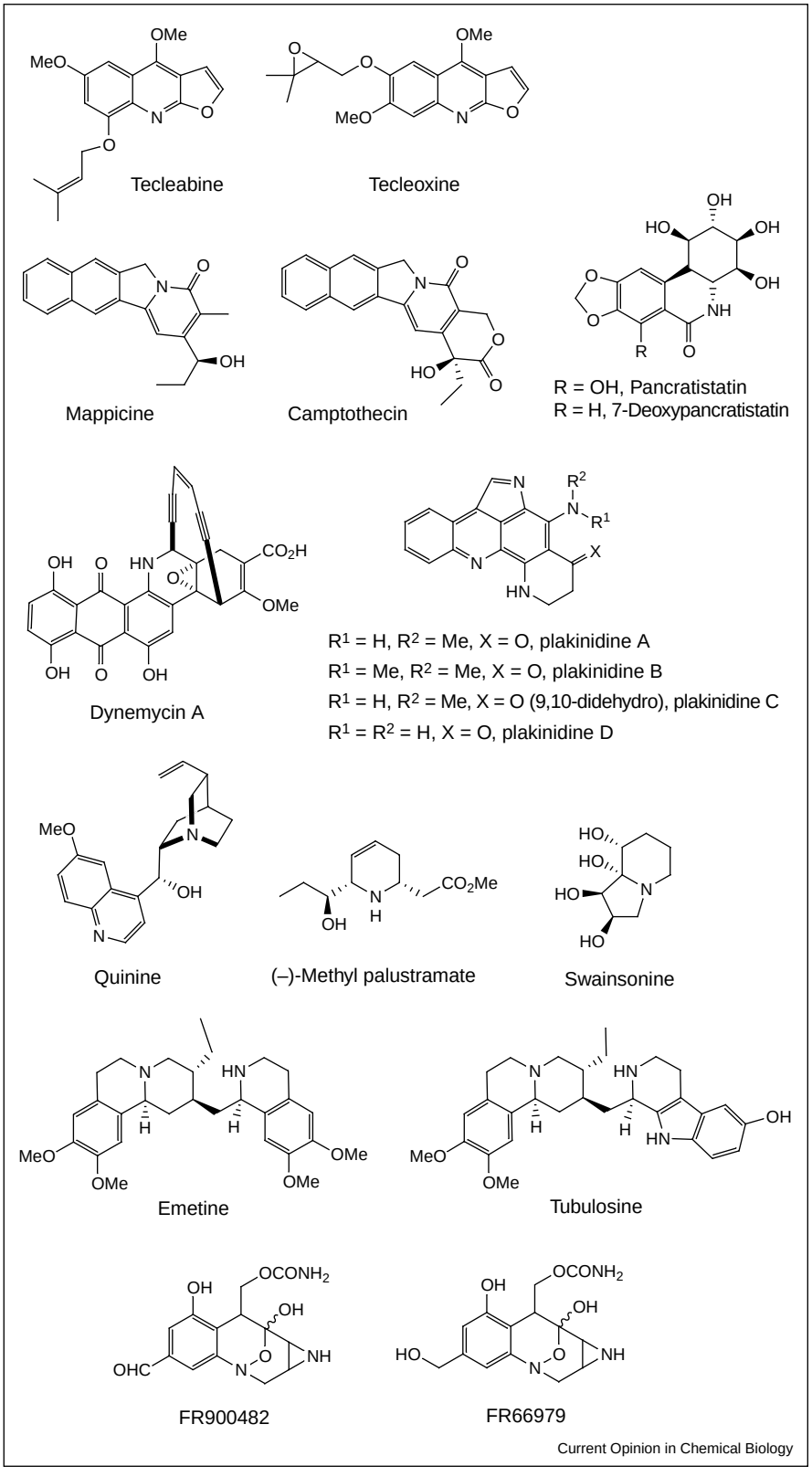
Although MCRs involving isocyanide substrates are very popular [6,7,9,11•], the commercial availability of these components is somewhat limited compared with common reagents such as aldehydes and amines. Despite this limitation, these processes can afford attractive polycyclic natural product-like scaffolds with surprising ease.

Furoquinoline alkaloids are one of the most common subclasses amongst quinoline alkaloids. Many members of this class exhibit interesting biological properties such as antimicrobial, antitumor and antiemetic activities [13–15]. Examples of furoquinoline alkaloids (tecleabine, tecleoxine) are shown in Figure 1.

The reported methods for the synthesis of this heterocyclic ring system tend to be linear and require harsh reaction conditions. To address these problems, Fayol and Zhu developed the conceptually novel isocyanide-based MCR depicted in Figure 2a [16•].

The generality of this operationally simple domino MCR between o-alkynyl anilines, aldehydes and isocyanoacetamides was studied in detail. Aniline derivatives bearing electron-poor and neutral acetylene units participate in this reaction. Aliphatic aldehydes, including sterically hindered ones, as well as aromatic aldehydes bearing electron-donating or withdrawing substituents can be incorporated. Different amino groups on the isocyanoacetamide (NR^4R^5) were found to be suitable, thus providing ample potential for introducing diversity with this

Figure 1



Examples of polycyclic natural products targeted using MCRs.