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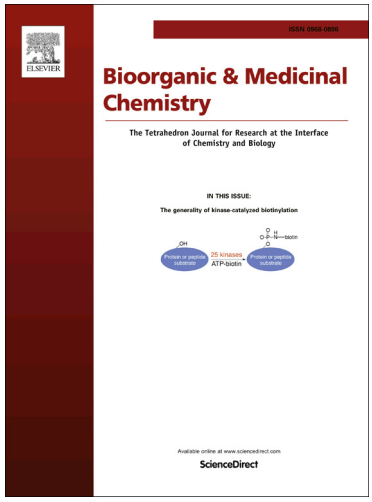

Construction of a 3D-shaped, natural product like fragment library by fragmentation and diversification of natural products

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Construction of a 3D-shaped, natural product like fragment library by fragmentation and diversification of natural products

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Abstract: A fragment library consisting of 3D-shaped, natural product-like fragments was assembled. Library construction was mainly performed by natural product degradation and natural product diversification reactions and was complemented by the identification of 3D-shaped, natural product like fragments available from commercial sources. In addition, during the course of these studies, novel rearrangements were discovered for Massarigenin C and Cytochalasin E. The obtained fragment library has an excellent 3D-shape and natural product likeness, covering a novel, unexplored and underrepresented chemical space in fragment based drug discovery (FBDD).

Introduction: Fragment Based Drug Discovery (FBDD) [1] has become a widely used method throughout pharmaceutical industry and academia demonstrating high impact on the discovery of low molecular weight drugs. [2-8] Traditionally, most fragment libraries are comprised of rather flat structures with only limited 3-dimensionality.[9-11] In contrast, saturation (sp^3 content) and presence of stereo centers increase, whereas aromatic ring count decreases during the transition from discovery through clinical trials to drugs.[12, 13] In addition, low nitrogen and high oxygen atom count were found to be associated with selective compounds.[13] Therefore, most fragment libraries do not match the properties displayed by marketed molecules making fragment optimization more difficult. As a result interest in fragment library design and especially generation of 3D-shaped and sp^3 rich libraries has been increased during the last years.[7, 9, 14-20]

Natural products comprise a rich source of compounds with diverse 3D-shapes and chiral centers, low aromatic ring and nitrogen count as well as high oxygen count, covering a chemical space often missing in current libraries.[21, 22] Therefore, we decided to assemble a fragment library inspired by natural products, aiming for 3D-shape and "natural product likeness" as measured by published algorithms.[23, 24]

In this report, we provide the general strategy and results of our efforts to generate a fragment library covering a novel chemical space defined by 3D-shape and "natural product likeness" In addition, we report associated novel chemistry on well-known natural products including Massarigenin C and Cytochalasin E.

Results and discussion: Efforts to obtain fragments were split into two three strategies, i) *in-silico* guided chemical disassembly of larger natural products, ii) chemical modifications of smaller natural products

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