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Total Synthesis of Hypermodified Epothilone Analogs

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1. ABSTRACT

Cancer represents one of the most severe health problems worldwide, and the search for improved cytotoxic agents constitutes an important part of modern anticancer drug discovery.

One promising class of anticancer agents are the epothilones (Fig. 1) which can be classified as tubulin inhibitors. They exert their activity by stabilization of microtubules, which eventually leads to programmed cell death in cancer cells. Since their discovery in 1987 and the elucidation of their mechanism of action in 1995, the epothilones have served as the lead structures for a vast number of SAR studies. The introduction of an epothilone analog (Ixempra®) into clinical cancer treatment (2008) has been the most tangible result of these extensive investigations to date.

![Figure 1: Naturally occurring epothilones, Epo A (1) and Epo B (2).](image)

While most of the SAR-studies were focused on the modification of single structural properties of the epothilone scaffold, it was the aim of this thesis to develop efficient synthetic access to epothilone analogs whose structure deviates strongly from the original natural product leads (structures of type T and Z, Fig. 2).

![Figure 2: Hypermodified epothilone target structures of this thesis.](image)
This new class of epothilones, which will be referred to as hypermodified epothilones throughout this thesis, differs from the natural epothilones in the nature and geometry of the three-membered ring fused to the C12-C13 bond (\textit{trans}-cyclopropane vs. \textit{cis}-epoxide), the structure of the C15 side chain, and by the lack of a hydroxyl group at C3. Compounds with even numbers bear an additional double bond. The synthesis of structures T1-T6 was based on a convergent concept with separate elaboration of an Eastern and a Western fragment (Fig. 3). Western fragment A3 could be accessed via an aldol reaction between \(\gamma\)-keto ester A2 and Roche ester-derived aldehyde A1.

An efficient synthesis of Eastern building blocks A6a,b,c was devised, which relied on enantioselective allylation and highly diastereoselective Charette cyclopropanation in the stereogenic steps. New methods were found that allowed the selective elaboration of the required cyclopropanated alkyl chain and provided alcohols A6a,b,c for coupling with acid A3. Subsequent to fragment coupling a highly \(E\)-selective RCM protocol was established to close the macrocycle leading to the protected precursor for the target structures of type T. Due to the fact that the syntheses of A6a,b,c were all equally efficient, independent of the nature of the bicyclic heteroaromatic moiety (benzimidazole, benzothiazole, quinoline) it is very likely that the methodology developed here will allow access to a range of other analogs of type T containing related benzo-fused heterocycles.

\[
\begin{align*}
\text{A1} & \quad + \quad \text{A2} \quad \rightarrow \quad \text{A3} \\
\text{A4a,b,c} & \quad \rightarrow \quad \text{A5a,b,c} \\
\text{A3} & \quad \rightarrow \quad \text{T1, T2: } R = \text{Me, } X = \text{NMe} \\
& \quad \text{T3, T4: } R = \text{Me, } X = \text{S} \\
& \quad \text{T5, T6: } R = \text{H, } X = \text{CH=CH}
\end{align*}
\]

\textbf{Figure 3}: Summary of the total synthesis of hypermodified epothilone analogs of type T.

All analogs of this type (T1-T6) investigated were found to be highly potent antiproliferative agents with IC\textsubscript{50} values for \textit{in vitro} cancer cell growth inhibition in the
low nM range, even against multidrug-resistant cell lines. As such, analogs T1-T6 may be considered as examples of a new structural class of microtubule-stabilizing agents, with the potential for an altered overall pharmacological profile relative to the original natural product leads. *In vivo* experiments are currently in progress with analog T1 to test this hypothesis.

The design of target structures Z was driven by the desire for a flexible synthetic route to hypermodified epothilone analogs that would enable the introduction of modified side chains at a late stage of the synthesis. This can be accomplished through the use of intermediate A13 (Fig. 4), for which an efficient route was developed. Key steps in the synthesis of A13 are the diastereoselective cyclopropanation in the synthesis of its Eastern building block A9 as well as diastereoselective aldol reaction between A10 and A11 which establishes the stereotriad C6, C7, C8 in the Western building block A12. As the first examples of analogs of type Z compounds Z1/Z2 were prepared through Wittig chemistry-based side chain attachment. Analog Z1 was found to be a potent antiproliferative agent with IC$_{50}$ values for *in vitro* cancer cell growth inhibition of 50-100 nM. In contrast, the corresponding 10,11-dehydro analog Z2 was virtually inactive. Based on existing SAR-data the activity of Z1 may be significantly improved by the replacement of the thiazole moiety by other heterocycles. Such analogs will be readily accessible by the chemistry developed in this thesis.

**Figure 4:** Summary of the total synthesis of hypermodified epothilone analogs of type Z.
2. ZUSAMMENFASSUNG


Abbildung 1: Natürlich vorkommende Epothilone, Epo A (1) und Epo B (2).

Während die meisten bisher durchgeführten SAR-Studien mit Epothilonen sich auf die Modifikation von einzelnen strukturellen Merkmalen beschränkten, war es das Ziel dieser Doktorarbeit, einen effizienten synthetischen Zugang zu Epothilonanologa, deren Struktur stark von den natürlich vorkommenden Leitstrukturen abweicht, zu entwickeln (Strukturen vom Typ T und Z, Abbildung 2).

Abbildung 2: Hypermodifizierte Epothilon-Zielstrukturen dieser Doktorarbeit.

Abbildung 3: Zusammenfassung der Totalsynthese von hypermodifizierten Epothilonaloga des Typs T.


Abbildung 4: Zusammenfassung der Totalsynthese von hypermodifizierten Epitholonanaloga des Typs Z.
zwischen 50 und 100 nM. Im Gegensatz dazu war die entsprechende 10,11-ungesättigte Verbindung \textbf{Z2} vollkommen inaktiv. Vor dem Hintergrund bereits vorhandener SAR-Daten für Epothilone, kann die Aktivität von \textbf{Z1} mit hoher Wahrscheinlichkeit durch das Ersetzen der Thiazolseitenkette mit anderen Heterozyklen deutlich erhöht werden. Derartige Analoga sind über die hier entwickelte Chemie zugänglich.