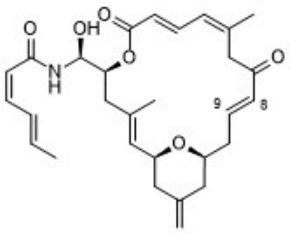
SAR of New Hetero-Monocyclic Analogs of (-)-Zampanolide

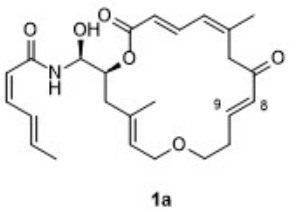
S. A. Glauser[1], K. Altmann[1]*

[1]ETH Zürich

The marine natural product zampanolide (**1**) acts as a potent microtubule inhibitor with binding at the taxane site on b-tubulin and it inhibits human cancer cell proliferation in vitro with single digit nM IC50 values. The structure of zampanolide (**1**) incorporates a highly unsaturated 20-membered macrolactone ring, an *N*-acyl hemiaminal-linked side chain, and a THP ring containing an exo-methylene group.[1]



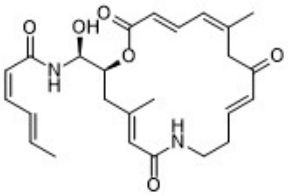
(-)-Zampanolide (1)



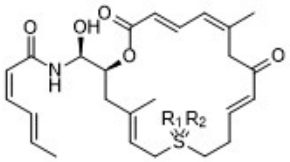
1a

Zampanolide binds to b-tubulin in a covalent fashion through 1,4-addition of His229 to the C8 – C9 double bond in the macrocycle. In contrast to the essential nature of the enone double bond, we have previously shown that the removal of the THP ring in zampanolide (**1**) is relatively well tolerated; thus, des-THP analog **1a** retains significant antiproliferative activity.[2] As part of a comprehensive project on the SAR of zampanolide-type structures, we have targeted various heteroatom-analogs of **1a** for synthesis (**2**-**8**), in order to evaluate if some the activity difference between **1** and **1a** could be recovered without a (re)increase in structural complexity.[3]

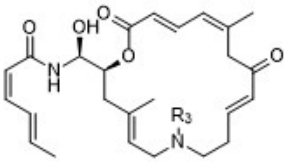
This contribution will discuss the synthetic chemistry of zampanolide analogs 2-8. In addition, the biological activity of selected compounds will be presented.



2



3: $R_1 = R_2 = X$
4: $R_1 = O$, $R_2 = X$
5: $R_1 = R_2 = O$



6: $R_3 = H$
7: $R_3 = Boc$
8: $R_3 = Ac$

[1] Jun-Ichi Tanaka, Tatsuo Higa, *Tetrahedron Letters*, **1996**, 37, 5535–5538.
[2] Didier Zurwerra, Florian Glaus, Leo Betschart, Julia Schuster, Jürg Gertsch, Walter Ganci, Karl-Heinz Altmann, *Chemistry - A European Journal*, **2012**, 18, 16868–16883.
[3] Andrea E. Prota, Katja Bargsten, Didier Zurwerra, Jessica J. Field, José F. Diaz, Karl-Heinz Altmann, Michel O. Steinmetz, *Science,* **2013**, 339, 587–590.