Synthesis of Analogs of (−)-Zampanolide and Structure-Activity Relationship Studies

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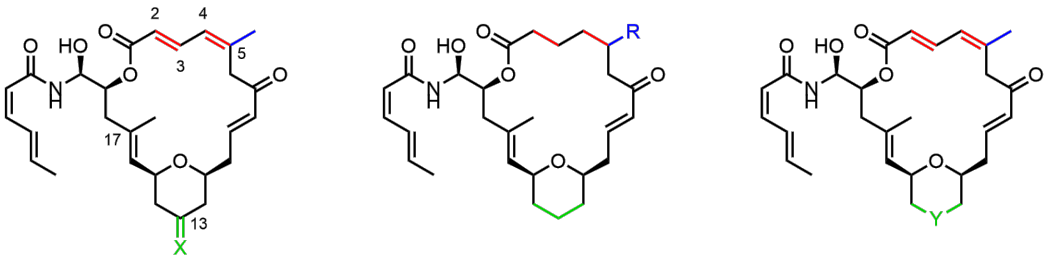
(−)-Zampanolide (**1**) is a complex marine macrolide that was first isolated from the sponge *Fasciospongia rimosa* in 1996 by *Tanaka* & *Higa* and found to exhibit nanomolar *in vitro* antiproliferative activity against a range of human cancer cell lines.[1]



The compound was subsequently shown to be a microtubule-stabilizing agent which, as the only potent microtubule stabilizer known, binds to β-tubulin in a covalent fashion.[2] (−)-Zampanolide (**1**) has been the target of several total synthesis campaigns,[3-7] including a synthesis developed in our own laboratory that is based on macrocycle formation by intramolecular HWE reaction.[8]

Our group has recently reported the fully stereoselective total synthesis of C(13)-desmethylene-(−)-zampanolide (**2**).[9] C(13)-Desmethylene-(−)-zampanolide (**2**) was found to be at least equipotent with natural **1**. Therefore, it has served as a more readily accessible template for SAR studies that aimed to address the importance of the various double bonds in the macrolactone ring, of the C(5) & C(17) methyl groups[10] and of the atom at position 13. This presentation will describe the synthesis of new analogs of **1**: with a fully saturated C(1) – C(5) domain (**3**), its C(5)-desmethyl variant (**4**)[10] and three analogs where carbon 13 is substituted by either oxygen (**5**) or sulfur (**6**) and its oxidized sulfone analog (**7**). In addition, their binding to microtubules and their cellular activity will be discussed.[10]

[1] J. I. Tanaka and T. Higa, *Tetrahedron Lett.* **1996**, 37, 5535–5538; [2] J. J. Field, A. J. Singh, A. Kanakkanthara, T. Halafihi, P. T. Northcote, J. H. Miller, *J. Med. Chem.* **2009**, 52, 7328–7332; [3] T. R. Hoye and M. Hu, *J. Am. Chem. Soc.* **2003**, 125, 9576–9577; [4] J. Uenishi, T. Iwamoto and J. Tanaka, *Org. Lett.* **2009**, 11, 3262–3265; [5] A. K. Ghosh and X. Cheng, *Org. Lett.* **2011**, 13, 4108–4111; [6] A. K. Ghosh, X. Cheng, R. Bai and E. Hamel, *European J. Org. Chem.* **2012**, 4130–4139; [7] A. B. Smith, I. G. Safonov and R. M. Corbett, *J. Am. Chem. Soc.* **2001**, 123, 12426–12427; [8] D. Zurwerra, F. Glaus, L. Betschart, J. Schuster, J. Gertsch, W. Ganci and K.-H. Altmann, *Chem. A Eur. J.* **2012**, 18, 16868–16883; [9] T. M. Brütsch, S. Berardozzi, M. L. Rothe, M. R. Horcajo, J. F. Diáz and K. H. Altmann, *Org. Lett.* **2020**, 22, 8345–8345; [10] T. M. Brütsch, E. Cotter, D. Lucena-Agell, M. Redondo-Horcajo, C. Davies, B. Pfeiffer, S. Pagani, S. Berardozzi, F. Diaz, J. H. Miller, K.-H. Altmann, *Chem. – A Eur. J.* **2023**, e202300703.