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Insights into the structure-activity relationship of the anticancer compound ZJ-101, a derivative of marine natural product superstolide A: a role played by the lactone moiety

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Abstract

Compound ZJ-101, a structurally simplified analog of the marine natural product superstolide A, was previously developed in our laboratory. In the subsequent structure-activity relationship study, a new analog ZJ-109 was designed and synthesized to probe the importance of the lactone moiety of the molecule by replacing the lactone in ZJ-101 with a lactam. The biological evaluation showed that ZJ-109 is about 8–12 times less active against cancer cells in vitro than ZJ-101, suggesting that the lactone moiety of the molecule is important for its anticancer activity.

Graphical Abstract

Keywords

Superstolide A analog; Anticancer agent; Structure-activity relationship; Drug design; Asymmetric synthesis

Over 70% of the earth's surface is covered by oceans, which contain numerous marine organisms with tremendous biological and chemical diversity. Over the last 30 years the marine environment has become the hot spot for the identification of biologically active natural products.¹ With more drugs from marine natural products approved by regulatory

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agencies for clinical uses and more entering clinical trials,² we are likely experiencing a 21st century renaissance of drug discovery based on marine natural products.³

We recently designed and synthesized a truncated superstolide A (named as ZJ-101) that maintains the potent anticancer activity of the original natural product superstolide A⁴ that was isolated in minute amounts from the deep-water marine sponge *Neosiphonia superstes* (Figure 1).⁵ Because our synthetic approach is efficient and the synthesis can be readily scaled up, we have produced sufficient amounts of material for additional biological and mechanistic evaluation.

ZJ-101 exhibited potent anticancer activity in the NCI-60 cell screen. The COMPARE pattern-recognition analysis of the NCI 60-cell mean graph screening profile of ZJ-101 does not show a strong correlation with any other known anticancer agents in the NCI's database, suggesting it likely has a novel and, as yet, undefined mechanism of action.⁶

While the potent anticancer activity of ZJ-101 partially confirmed our original hypothesis that the 16-membered macrolactone is likely the pharmacophore responsible for interacting with its putative target,⁵ it is imperative to precisely characterize the role of several key functionalities in ZJ-101 on the anticancer activity. Our recent structure-activity relationship studies have shown that the cyclohexenyl group and the double bonds between C2–C3 and the C4–C5 of the trienyl conjugated lactone moiety are important for its anticancer activity.⁷

To investigate the role of the lactone moiety on the anticancer activity, we designed analog ZJ-109 (Figure 2) where the lactone is replaced with a lactam. This analog would not only enable us to gain insights on the structure-activity relationship of ZJ-101 but also reveal the significance of the lactone moiety on the anticancer activity. Moreover, ZJ-109 may have preferable DMPK properties over ZJ-101. Herein, we report our synthesis and biological evaluation of compound ZJ-109.

The retrosynthetic analysis of ZJ-109 is analogous to that of ZJ-101 and is outlined in Scheme 1. This synthetic route is advantageous as it is flexible and convergent.

The commercially available *N*-Boc-D-alanine methyl ester **7** was converted to compound **8** using reported procedures (Scheme 2).⁸ Compound **8** underwent Lemieux-Johnson oxidation⁹ to give aldehyde **9** in 89% yield. Crotylboration between compound **9** and (*Z*)-crotyldiisopinocampheylborane derived from (–)-*B*-methoxydiisopinocampheylborane ((–)-IpC₂BOMe) afforded homoallylic alcohol **10** in 75% yield using Brown's conditions¹⁰ and the workup-purification procedure developed in our laboratory.¹¹ The stereochemistry of compound **10** was assigned on the basis of literature precedents.¹⁰ Compound **10** was converted to compound **11** in 92% yield under Mitsunobu conditions. It should be noted that hydrazoic acid is dangerously explosive and its solution should be handled with extra care. The reaction should be carried out behind a blast shield. Azide **11** was reduced by L-selectride and the resulting amine was protected by a trimethylsilylethoxy-carbonyl (Teoc) protecting group to provide compound **12** in 81% yield. Cross metathesis reaction between compound **12** and pinacol vinylboronate gave *trans*-vinyl boronate **5** in 49% yield.¹²

Fragment **5** reacted with fragment **4** under Suzuki conditions to afford compound **13** in 43% yield with complete stereoselectivity (Scheme 3).⁵ Negishi coupling between vinyl bromide **13** and dimethylzinc provided the requisite trisubstituted olefin **14** in 82% yield with complete stereoselectivity.⁵ The triethyl silyl group in compound **14** was removed chemo- and regioselectively by 1 equivalent of TBAF to give compound **15**, which underwent a regio- and stereoselective hydrostannylation to afford *trans*-vinyl stannane **16** in 70% yield. The trimethylsilylethoxycarbonyl (Teoc) protecting group was cleaved by TBAF and the resulting amine reacted with fragment **6** to furnish amide **17** in 93% yield. Compound **17** underwent an intramolecular Stille coupling to give the 16-membered lactam **18** in 64% yield.⁵ Removal of both Boc and oxazolidine protecting groups under acidic conditions followed by chemoselective acylation of the resulting amine provided ZJ-109 in 71% yield.

The antiproliferative effects of ZJ-109 were determined in MDA-MB-231 (human breast cancer), SF-295 (human glioblastoma), MCF-7 (human breast cancer), HCT-116 (human colon cancer) and HeLa (human cervical cancer) cell lines using the Alamar Blue viability assay, along with ZJ-101 as the positive control.¹⁵ The IC₅₀ values are shown in Table 1. The data showed that the antiproliferative activity of ZJ-109 is about 8–12 times less than ZJ-101 in these five cell lines, suggesting that the lactone moiety is important for its biological activity.

In conclusion, we have designed and synthesized compound ZJ-109 by replacing the lactone moiety in ZJ-101 with a lactam. The biological testing has confirmed our original hypothesis that the trienyl conjugated lactone moiety of the molecule is indeed the pharmacophore and future structural optimization should keep the chemical structure of this region intact. Research in this direction is currently underway and will be reported in due course.

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Conflict of interest statement

Dr. Zhendong Jin is the founder and a shareholder of InnoBioPharma, LLC that sponsored the project, “Development of novel anticancer agents based on natural products” at the University of Iowa.

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Figure 1.
Superstolide A and truncated superstolide A (ZJ-101)

Figure 2.
Designed analog ZJ-109

Scheme 1.
Retrosynthetic analysis of ZJ-109

Scheme 2.
Synthesis of compound **12**

Scheme 3.
Synthesis of ZJ-109

Table 1

Antiproliferative effect of ZJ-105 and ZJ-106 on various malignant tumor cells (Alamar Blue assay)

Entry	Cell Line	ZJ-109 IC ₅₀ (nM)	ZJ-101 IC ₅₀ (nM)
1	MDA-MB-231	584.2	63.04
2	SF295	716.3	63.48
3	MCF-7	447.7	36.54
4	HCT-116	746.5	94.02
5	HeLa	596.7	75.44