Apratoxin S10, a Dual Inhibitor of Angiogenesis and Cancer Cell Growth to Treat Highly Vascularized Tumors

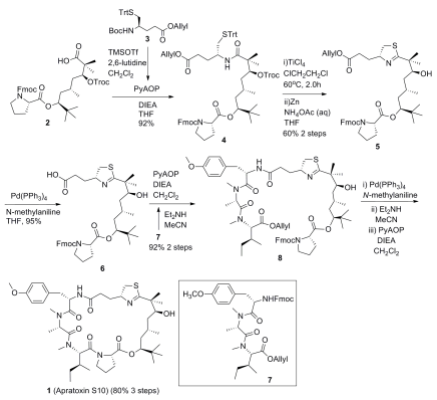
Cai, W., Chen, Q.-Y. (UF, Med. Chem.); Dang, L.H. (UF, Medicine); Luesch, H. (UF, Med. Chem.)

Introduction

Vascular endothelial growth factor A (VEGF-A) is the key angiogenic regulator contributing to tumor angiogenesis through binding to VEGFR2. Although many VEGF-targeted therapies have been used in clinic, drug resistance are frequently observed. There is significant relationship between interleukin 6 (IL6) and both tumor angiogenesis and tumor resistance against antiangiogenic therapies. In addition, therapies that possess both antitumor and antiangiogenesis activities would be beneficial to circumvent the acquired resistance. We previously discovered a group of potent anticancer agents, apratoxins, which have the potential as dual inhibitors due to its ability to block cotranslational translocation at the level of Sec61. Here we proposed a new analogue, apratoxin S10 (**1**), to achieve a balance between potency, synthetic yields and stability.

Results and Discussion

Synthesis. **Scheme 1** displays the later stage total synthesis of apratoxin S10. Staring from acid **2,** via sequential reactions including coupling with the amine from moCys Kelly's reaction to construct thiazoline ring, coupling with tripeptide **7** and macrocyclization, **1** was obtained in 80% yield in final three steps and 4.5% total yield, both of which are higher than that of apratoxin S8. The better yields were also found in the synthesis of other intermediates. The NMR spectra of **1** were achieved by the Bruker Advance II 600 in AMRIS, UF.



Scheme 1. Total Synthesis of Apratoxin S10

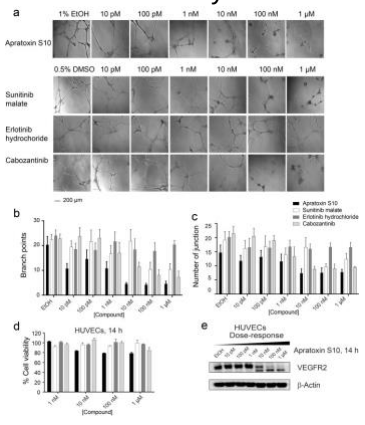


Fig 1. Apr S10 inhibited angiogenesis

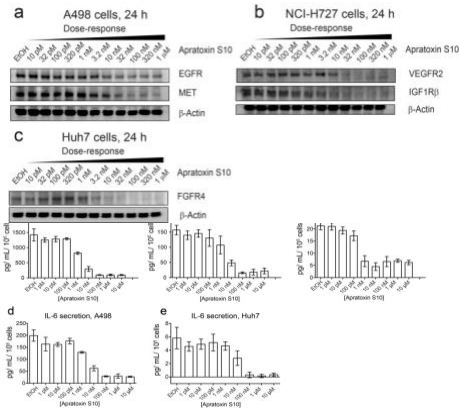


Fig 2. (up) Activity of apratoxin S10 on VEGF-A IL-6 secretion I; (down) mmunoblot analysis of apratoxin S10 on three cell lines

Bioassay. Apra S10 possess improved antiproliferative activity against HCT116 (IC_{50} = 1.47 nM) and good stability. It showed potent antiangiogenic effect in an in vitro angiogenesis model and it down-regulated the VEGFR 2 expression in endothelial cells (Fig 1); VEGF-A from three cell lines, A498, Huh7 and NCI-H727, was blocked by apra S10 (Fig 2 up); and IL6 from the former two cell lines was effectively inhibited too (Fig 2 down).

Conclusions

We total synthesized a novel apratoxin analogue, apratoxin S10, which is considered one of the lead candidates of the apratoxin family in terms of potency, stability, and synthetic accessibility. Apratoxin S10 inhibited angiogenesis in vitro through down-regulation of VEGFR2 expression of endothelial cells and blocked secretions of VEGF-A and IL-6 from cancer cells, which are triggers for blood vessel formation. It also showed potent inhibitory effects against cancer cells from highly vascularized tumor through down-regulations of multiple RTKs.

Acknowledgements

A portion of this work was performed at the National High Magnetic Field Laboratory, which is supported by National Science Foundation Cooperative Agreement No. DMR-1157490 and the State of Florida.
This research was supported by the National Institutes of Health grant R01CA172310 and Ocala Royal Dames for Cancer Research, Inc.

References

Cai, W., *et. al*. *ACS Med. Chem. Lett*. **2017**, 8, 1007-1012.