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Progress Toward Synthetically Simplified Natural Anticancer Peptide

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# Yaku'amide A (YA) was isolated in late 2010 from the deep-sea sponge Ceratopsion sp. and exhibits potent inhibitory activity against 39 human cancer cell lines via a potentially novel mode of action. However, the total synthesis requires many steps and produces low yields.

## HYPOTHESIS

In this study, we determined two simpler YA analogues (F and H) that retain its anticancer properties and can be synthesized in larger quantities. The analogues replace dehydroisoleucine (\(\Delta Ile\)) with either dehydroethylnorvaline (\(\Delta Env\)) or dehydrovaline (\(\Delta Val\)).

### DISCUSSION

We identified two analogues, F and H, that are similar to Yaku'amide A. The predicted structure is divided into two sections. One half is flexible and the other half is tightly held by intramolecular hydrogen bonding. Such features may play a role in its activity. The identification of YA analogues will make YA accessible to future anticancer research and expedite interdisciplinary studies of its mechanism.

## COMPUTATIONAL RESULTS

The Root Mean Square Deviation (RMSD) calculations show that analogues F and H (Figure 2 and 3.B) are most similar to Yaku'amide A. Analogue F performed best across all calculations and is superposed against Yaku'amide A in figure 3.B to show similarity. Thus, analogue F is the most promising candidate for a Yaku'amide-based anticancer drug.

### FIGURE 3. RESULTS OF CALCULATIONS

Our calculations also provide the first insights into the structure of YA, which could lead to a better understanding of its anticancer activity. Our three quantum mechanical studies converged on the same conformation (Figure 4A), where one half has well-defined hydrogen bonding and the other is more flexible (Figure 4B). The first step to understanding Yaku’amide’s novel anticancer properties is to understand it’s shape.

### FIGURE 4. THE STRUCTURE OF YAKU’AMIDE A

From among the original eight analogues, F and H are the most promising candidates for future Yaku’amide-inspired anticancer drugs. Quantum mechanic/ molecular mechanic simulations predict that F and H have structures most similar to that of Yaku’amide.