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Spotlights on Recent *JACS* Publications

20-STEP SYNTHESIS OF AN *ALSTONIA SCHOLARIS* INDOLE ALKALOID

In traditional Chinese medicine, the leaves of *Alstonia scholaris* have been used to treat chronic respiratory diseases. Scholarisine A, a monoterpenoid indole alkaloid first isolated in 2008, is one of almost 400 tryptophan-based alkaloid *Alstonia* sp. natural products identified to date. While the biological activity of scholarisine A has yet to be determined, the unique lactone-containing cage structure in this molecule comprises a challenging synthetic target.

Amos B. Smith III and Greg L. Adams have achieved the first total synthesis and assignment of the absolute configuration of the architecturally complex compound (+)-scholarisine A. The synthesis included a number of key features (DOI: 10.1021/ja211840k). First, a reductive cyclization cascade was employed to form the cage-shaped tricyclic intermediate, a distinctive feature of this natural product. A Fischer indolization inspired by work from the early 1970s sets the groundwork to generate the indolenine in the natural product after a late-stage oxidative cyclization to form the lactone.

Diverse synthetic chemistry permitted the researchers to achieve this total synthesis, and extensive X-ray analysis allowed them to confirm the absolute stereochemical configuration of the natural product. These efforts may permit scientists to determine whether this compound—like a related precursor—inhibit SGLT2, a protein being studied in relation to type-II diabetes. **Sonja Krane, Ph.D.**

BULGES IN REPETITIVE DNA CAN MOVE AROUND, INFLUENCING DNA EXPANSION, RECOGNITION, REPLICATION, AND REPAIR

More than 30 genetic disorders, including Huntington's disease and myotonic dystrophy type 1, stem from mutations that result in expanded stretches of DNA. Long stretches of repeating three-base DNA sequences, such as CAG or CTG called triplet repeats, are prone to expansion. How these repetitive regions become dangerously long is not well understood.

Sometimes a section of these sequences will bulge out and form a loop. It is hypothesized that bulge loops play an important role in DNA expansion processes. Kenneth Breslauer and his colleagues learned that within triplet repeat domains bulge loops can move around and adopt several positional isomers, which they call rollamers (DOI: 10.1021/ja3010896). Using fluorescence, absorbance, and calorimetric measurements, the team demonstrated that rollamers can migrate within a repetitive region of DNA. They also showed that defects in the DNA strand called abasic lesions, a common type of DNA damage, influence the position of the rollamers.

Enzymes that modify and copy DNA molecules can be tripped up by rollamers. Therefore, knowing that these loops can move around, and understanding the factors that influence their motion, will help researchers to understand DNA expansion mutations within the long repetitive sequences associated with a variety of human genetic diseases. **Aaron Rowe, Ph.D.**

PROFILING AN ELUSIVE ENZYME SUPERFAMILY

Human cells contain approximately 20 000 different proteins, a grouping collectively referred to as the proteome. About 1% of the proteome comprises a class of enzymes called serine hydrolases, which play important roles in numerous biological processes such as blood clotting, digestion, and signaling in the brain. In addition, many drugs for conditions like type 2 diabetes, obesity, and Alzheimer's disease work by disrupting the activity of serine hydrolases. Despite their importance, the specific functions of most serine hydrolases are not well understood.

Now, Gregory Fu, Benjamin Cravatt, and co-workers report the discovery of a chemical scaffold—an aza-β-lactam—that selectively interacts with serine hydrolases (DOI: 10.1021/ja300799t). Using a strategy called activity-based protein profiling, aza-β-lactams were added to proteomes from cells or tissues, enabling the enzymes that interacted with them to be isolated and identified. Structurally related to β-lactam antibiotics like penicillin, aza-β-lactams were found to inhibit several serine hydrolases and, in some cases, these interactions were selective for individual serine hydrolases over others.

This study reveals aza-β-lactams as exciting new molecular tools for probing the many roles that serine hydrolases play in biology. These compounds will help clarify the functions of serine hydrolases and also serve as important starting points for the discovery of new drugs that target this enzyme superfamily. **Eva J. Gordon, Ph.D.**

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