Studies in Natural Products Chemistry: Chapter 1. Bioprospecting in the Berkeley Pit: The Use of Signal Transduction Enzyme Inhibition Assays to Isolate ... Fungi of an Acid Mine Waste Lake

Andrea A. Stierle, Donald B. Stierle

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The search for extremophiles conjures the image of daring adventurers exploring dramatic geologic or climatologic phenomena. Berkeley Pit Lake, however, is not buried deep in the ocean, cradled in a volcanic caldera, or marooned at the southern tip of Antarctica. Instead, it is nestled in a mineral-rich formation in the Rocky Mountains in Butte, Montana. The Berkeley Pit evolved from an open-pit copper mine to an acid mine waste lake in less than 20 years. Today, Berkeley Pit Lake is part of the largest Superfund site in the USA. The Environmental Protection Agency and Montana residents view the Berkeley Pit as an ecological time bomb, but it is something more—an evolving and dynamic ecosystem, a classic by-product of the industrial age. Although conditions within the Pit Lake system are toxic for “normal” aquatic biota, these same conditions provide an ideal environment for extremophiles. Since 1995, we have isolated over 60 fungi and bacteria from the waters and basal sediments of the Pit Lake. Specific signal transduction enzyme inhibition assays were used to guide the isolation of bioactive secondary metabolites from broth cultures of selected microbes. Compounds that were isolated based on their ability to inhibit matrix metalloproteinase-3 have demonstrated selective activity against specific cancer cell lines in the National Cancer Institute's human cancer cell line screen. Caspase-1 inhibitors have shown selective cytotoxicity toward leukemia cell lines and have demonstrated the ability to mitigate the production of proinflammatory cytokines in induced inflammasome assays. This review describes the compounds isolated from this hostile environment and compares them to secondary metabolites isolated from other acid mine waste lakes.

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