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Activity-driven discovery of Brazilian biodiversity using native metabolomics

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Natural products are a valuable resource for discovering and developing new drugs. The main challenge in this process is identifying compounds that act on specific targets. One way to overcome this challenge is through targeted metabolomic screening. Native metabolomics, a mass spectrometry-based method, has emerged as a promising way to identify compounds in complex matrices that can interact with specific protein targets on a large scale. BR177, a marine actinomycete isolated off the Brazilian coast, showed promising results regarding the anti-tumor activity of its extracts. However, the targets and modulators of this activity have not yet been fully elucidated. Therefore, we hypothesized that one or more metabolites could act on proteases, thereby triggering the observed effect on tumor cells. To test this hypothesis, we used native metabolomics to evaluate the potential of bioactive compounds in the exometabolome of BRA177 on chymotrypsin, a model serine protease. Two metabolites, among 2,197 detected features, interacted with chymotrypsin. Based on their fragmentation spectra, we annotated both compounds as riboflavin, a pteridine, and a terpenoid derived from glucopyranosiduronic acid. Through docking, both compounds demonstrated binding capacity with the target protein in all described isomers of riboflavin and three of the five described isomers of the terpenoid derivative. These results demonstrate the potential of native metabolomics as a platform for the directed discovery of new bioactive candidates from complex matrices, with a focus on Brazilian diversity.

Keywords: *Mass spectrometry; Guided-discovery approach; Native metabolomics*