

Novel 2-benzoyl-6-(2,3- dimethoxybenzylidene)-cyclohexenol confers selectivity toward human MLH1 defective cancer cells through synthetic lethality

ABSTRACT

DNA mismatch repair (MMR) deficiency has been associated with a higher risk of developing colorectal, endometrial, and ovarian cancer, and confers resistance in conventional chemotherapy. In addition to the lack of treatment options that work efficaciously on these MMR-deficient cancer patients, there is a great need to discover new drug leads for this purpose. In this study, we screened through a library of commercial and semisynthetic natural compounds to identify potential synthetic lethal drugs that may selectively target MLH1 mutants using MLH1 isogenic colorectal cancer cell lines and various cancer cell lines with known MLH1 status. We identified a novel diarylpentanoid analogue, 2-benzoyl-6-(2,3-dimethoxybenzylidene)-cyclohexenol, coded as AS13, that demonstrated selective toxicity toward MLH1-deficient cancer cells. Subsequent analysis suggested AS13 induced elevated levels of oxidative stress, resulting in DNA damage where only the proficient MLH1 cells were able to be repaired and hence escaping cellular death. While AS13 is modest in potency and selectivity, this discovery has the potential to lead to further drug development that may offer better treatment options for cancer patients with MLH1 deficiency.

Keyword: Cancer; Diarylpentanoid; Mismatch repair; Synthetic lethality