Public Abstract
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Title:HYPOXIA-SELECTIVE ANTITUMOR PRODRUGS AND FLUORESCENT PROBES

Hypoxia-selective antitumor prodrugs utilize the unique feature of most tumors – hypoxia (low oxygen concentration), for therapeutic purpose and are widely studied in preclinical and clinical stages. Tirapazamine (TPZ, 3-amino-1,2,4-benzotriazine-1,4-di-N-oxide) is a hypoxia-selective cytotoxin that has been examined in Phase II and III clinical trials. The mechanism of DNA strand cleavage by TPZ and its analogs is still unknown. We described two isotopic labeling studies followed by MS analysis to explain the DNA strand cleavage of TPZs. One is to use desamino TPZ (1,2,4-benzotriazine 1,4-di-N-oxide) to provided evidence against the generation of benzotriazinyl radical intermediates. The other one is to use 18O-labeled TPZ and DMSO-diazonium salt derivatization to provide direct evidence for the generation of hydroxyl radical.

At least two conditions are required for successful clinical application of hypoxia-selective prodrugs: i. target tumors must be hypoxic and ii. appropriate enzymes involved in bioactivation of the drug must be expressed in the tissue. In this regard, it will be necessary to develop diagnostic probes to assess the expression of these enzymes. Here we described tirapazamine analogs as pro-fluorescent substrates of enzymes that catalyze the bioreductive activation of hypoxia-selective prodrugs. That is, the reduced metabolites generated by one-electron enzymatic activation of these compounds under hypoxic condition are fluorescent, while the parent compounds are non-fluorescent. Our results could facilitate the development of useful fluorescent probes in detecting one electron reductases involved in bioactivation of hypoxia-selective antitumor prodrugs.