Public Abstract
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Title:Metabolically Activated Heterocyclic N-Oxide Compounds for Killing and Visualizing Hypoxic Cancer Cells

Tirapazamine (TPZ) is an experimental prodrug for the treatment of various human cancers. TPZ shows its cytotoxicity selectively in the solid tumors. TPZ derives its medicinal activity by inducing DNA damage in poorly oxygenated tumors. Selective bioreductive enzymatic metabolism of TPZ in tumor cells leads to radical intermediates, which primarily contribute oxidative DNA damage. The nature of radical intermediates responsible for DNA damage is still a matter of debate. At the same time, there is an ongoing effort to prepare TPZ analogues as potential new antitumor agents. Thus, there is immediate need for the development of synthetic methods for the preparation of TPZ analogues. To address these problems, we have synthesized a series of heterocyclic N-oxide compounds which are structurally similar to antitumor agent TPZ. We have discovered some of the compounds damage DNA under bioreductive hypoxic conditions, which are characteristics of solid tumors. We reinvestigate the mechanism of TPZ action, and our data support the release of a hydroxyl radical from activated TPZ is responsible for DNA damage. This information is critical to our understanding of the effect of anticancer agent TPZ on various solid tumors. In addition to this work, we have discovered for the first time the chemistry of the benzotriazine scaffold as a hypoxia-selective fluorescent probe. This finding with the aid of technology may be useful in facilitating hypoxia-directed imaging in cancer therapy.