ABSTRACT

Tirapazamine (TPZ) is currently undergoing a variety of phase I, II, and III clinical trials for the treatment of various human cancers. TPZ derives its medicinal activity by inducing DNA damage in poorly oxygenated tumor cells. 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.

The very first part of this dissertation provides the utility of Suzuki coupling in the synthesis of 3-alkyl and 3-aryl derivatives of the antitumor agent TPZ. In these studies, the bromo substrate provided improved yields that chloro. To the best of our knowledge, we have provided general scope of Suzuki coupling reaction on the benzotriazine-1-oxide substrates involving various 3-aryl, and 3-cyclopropyl boronic acid to build a series of TPZ analogues.

In addition to this work, we prepared novel 3-cyclopropyl-1,2,4-benzotriazine 1,4-dioxide which damages DNA under bioreductive hypoxic conditions. We also, utilized another 3-alkyl derivative of TPZ, 3-methyl-1,2,4-benzotriazine-di-*N*-oxide, to reinvestigate the mechanism of TPZ action. Our data imply the release of hydroxyl radical from activated TPZ is a reasonable mechanism to explain the DNA damage. This information is critical to our understanding of the effect of anticancer agent TPZ on various solid tumors

We also show for the first time that other class of heterocyclic *N*-oxides such as natural product myxin and methylmyxin behave like redox activated hypoxia selective DNA damaging agent tirapazamine.

In the last part of this thesis, we have explored for the first time the chemistry of the benzotriazine scaffold as a hypoxia-selective fluorescent probe. We have studied with a series of known benzotriazine compounds, and have found a few with a moderate fluorescence quantum yield and molar extinction coefficient. Our novel effort toward hypoxia directed fluorescent small molecule probes may be useful for imaging in cancer therapy, and other hypoxia related diseases.