CHEMICAL MECHANISMS UNDERLYING THE MEDICINAL ACTIVITY OF METABOLICALLY-ACTIVATED $N$-OXIDE ANTITUMOR AGENTS

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ABSTRACT

Tirapazamine (TPZ) belongs to a new class of bio-reductively activated hypoxia-selective anti-cancer agents and is currently undergoing in various clinical trials including Phase I, II and III. Anti-cancer activity of TPZ derives from its ability to cause the DNA strand cleavage in oxygen poor environment found in solid tumors. However, the exact nature of DNA damaging agent produced from activated TPZ is not well understood.

In our studies, we carried out systematic mechanistic studies to understand the exact nature of DNA damaging agent(s) produced from enzymatically activated TPZ and structurally similar heterocyclic di-oxides. Our data shows that TPZ and its related di-$N$-oxides release known DNA damaging agent hydroxyl radical. Thus, our data suggests that TPZ and its analogs deliver known radiotherapeutic DNA damaging agent hydroxyl radical under oxygen poor environment found in solid tumors.