Development of Novel Small Molecules as Potential Anti-Cancer Agents

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Abstract

For the past several years at Rowan University, we have been involved in the development of novel small molecules such as benzoboroxoles and betulinic acid derivatives as potential anti-cancer agents.

Betulin and betulinic acid are triterpenoid natural products, which can be readily extracted in high quantities from external bark of yellow and white birch trees. Birch tree is native to North America and is also commonly available for purchase as firewood. Betulinic acid is found to exhibit very good activity against few cancer cell lines, and is relatively non-toxic to normal cells. The ready availability and selective cytotoxicity coupled with the favorable therapeutic index have made betulinic acid an attractive and promising *anti*-cancer agent. However, this molecule is almost insoluble in water and shows toxicity only on very few cancer cell lines. We have undertaken a systematic study involving the synthesis and biological evaluation of betulin derived small molecules in an effort towards improving the water solubility as well as the therapeutic profile of the parent natural product.

The successful induction of bortezomib (Velcade®) as a proteasome inhibiting *anti*-cancer drug for treatment of multiple myeloma and of tavaborole (Kerydin®) as a *Leucyl-tRNA synthetase* inhibitor for the treatment of onychomycosis has invigorated the exploration of boron based small molecules as therapeutic agents. Boronic acids are extremely valuable boron compounds that have applications in medicinal and materials chemistry as well as in reaction methodology development. *B*-hydroxy-1, 2-oxaborolanes (benzoboroxoles) are a subclass of bicyclic boronic acids that have received wide attention in the recent literature owing to their structural stability and synthetic utility. Our long-standing interest in developing novel functionalized benzoboroxoles as therapeutic agents prompted us to explore the utility of these scaffolds as potential *anti*-cancer agents.

Based on these studies, we have been able to identify few lead derivatives for further *in vivo* assays. The talk will focus on our synthetic and biological evaluation data in these projects.