Structure-Activity Relationship Studies of Arylnaphthalene Lignan Lactones and Protein Target Elucidation

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Arylnaphthalene lignan lactones, a class of natural products isolated from plants in the Phyllanthaceae family, have been found to display a diverse range of antitumor, anti-inflammatory, and antiviral properties. Through structural manipulation, efforts have been made to increase the potency and probe the mechanism of action of various members of this class, although a definitive protein target has remained somewhat elusive. Recently, the Kinghorn lab reported the isolation of two related series of arylnaphthalene lignan lactones, the phyllanthusmins and the acutissimalignans from *Phyllanthus poilanei* and *Phyllanthus songboiensis*, respectively. These natural products, which showed promising cytotoxicity in a number of cancer cell lines, served as lead compounds for a thorough structure-activity relationship analysis that led to the development of the highly potent compound PHY-34. PHY-34 has shown low- to sub-nanomolar potency in several solid-tumor cell lines and promising *in vivo* data in an OVCAR8 xenograft model[1]. Subsequent optimization of PHY-34 has focused on selective functionalization of the glycone portion of PHY-34 to probe cell line selectivity, increase stability, and develop mechanistic probes[2,3]. Comparison of NCI 60 profiles and analysis of *in vitro* efficacy in a series of cell lines developed by Novartis has been carried out, suggesting that these compounds interact with the membrane-associated ATP6V0A2 subunit of the vacuolar ATPase (v-ATPase).

References:

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The authors would like to gratefully acknowledge Jason Thomas and Markus Schirle for their assistance in assay development and execution.