Synthesis and Structure-Activity Relationships of Benzothienothiazepinone Inhibitors of Protein Kinase D

Published date: Aug. 28, 2016

Technology description

Protein kinase D (PKD) is a member of a novel family of serine/threonine kinases that regulate fundamental cellular processes. PKD is implicated in the pathogenesis of several diseases, including cancer. Progress in understanding the biological functions and therapeutic potential of PKD has been hampered by the lack of specific inhibitors. The benzoxoloazepinolone CID755673 was recently identified as the first potent and selective PKD inhibitor. The study of structure-activity relationships (SAR) of this lead structure led to further improvements in PKD1 potency. The innovators have developed a synthesis and biological evaluation of novel benzothienothiazepinone analogs. A ten-fold increase in the in vitro PKD1 inhibitory potency for the second generation lead kb-NB142-70 has been achieved. A transition to an almost equally potent novel pyrimidine scaffold has been accomplished. These promising results will guide the design of pharmacological tools to dissect PKD function and pave the way for the development of potential anti-cancer agents.

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