Isozyme-Specific Covalent Inhibitors of Oncogenic Kinase Akt

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Technology description

This invention comprises novel isozyme-specific covalent inhibitors of oncogenic kinases Akt2 and 3. Akt is a serine/threonine kinase with different isoforms that mediate essential signaling in cellular responses. Moreover, certain cancers have been associated with the overexpression of specific isozymes of Akt – Akt2 overexpression in breast cancer cells leads to increased invasiveness and metastasis, whereas upregulation of Akt3 contributes to steroid-independent breast and prostate cancer progression. However, current Akt inhibitors, such as MK2206, currently in Phase 2 clinical trials, GSK690693 and inhibitor VIII are not isozyme specific and are reversible. As such, there is a need for covalently bound isozyme-specific Akt inhibitors to minimize undesired impacts on the activity of other isozymes that are present in healthy cells.

Using proprietaryin situelectrophile-sensitivity screens (T-REX and G-REX), it was discovered that Akt 3 is a first-responding isozyme which senses native electrophilic lipids such as 4-hydroxynonenal (HNE). This discovery enabled the rational drug design of MK2206-HNE analogues which (i) specifically targeted redox-sensing cysteine residues of Akt 2 and 3, but not Akt 1; and (ii) whose binding was covalent.

These novel inhibitors further demonstrate the need to continue to identify and target innate electrophile-sensing residues for the development of covalent drugs using assays such as G-REX.

Additional Information

D- 7884: : G-REX toolbox.

Marcus J. C. Long, and Yimon Aye. (2017). Privileged Electrophile Sensors: a Resource for Covalent Drug Development.Cell Chemical Biology. Cell Chemical Biology 24, July 20, 2017 .

Marcus J. C. Long, & al. (2017). Akt3 is a Privileged First Responder in Isozyme-Specific Electrophile Response. Nature Chemical Biology13, 333–338 .

Application area

Lead therapeutic compounds to target Akt isozymes 2 and 3

Valuable research tools to study Akt kinases

Advantages

Isozyme specific
Covalent binding to reduce off-target effects

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