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Prodrugs of PKC modulators for improved formulation, therapeutic efficacy and tolerability

Researchers at Stanford have developed prodrug derivatives of protein kinase C (PKC) modulators that have lower toxicity and are more effective than the parent compound. PKC modulators are being developed to treat a variety of diseases. However, these drugs have problems that may limit their use clinically; including difficult formulations, stability and toxicity issues and non-optimal efficacy. To overcome these problems the inventors have developed this technology which provides novel prodrugs of PKC modulators as well as methods for the design and synthesis of such prodrugs. The prodrugs extend the therapeutic window and have increased efficacy and decreased toxicity as compared to the parent compounds and thus may serve as superior therapeutics.

Stage of research
The prodrugs have been shown to be effective in cells and live animals. Additional development is ongoing.

Applications

- PKC modulator prodrugs as therapeutics for:
    - HIV/AIDS
    - Cancer
    - Alzheimer's disease
    - Other neurological disorders such as:
        - Fragile X syndrome
        - Neimann-Pick disease
        - Charcot-Marie-Tooth disease

Advantages

- More active than parent compounds, with lower toxicity
- Allows sustainable release of free drug over a long period of time
- Improved therapeutic window
- Can be used to treat a variety of diseases
- Synthesis is concise and allows for easy derivatization to prepare other analogs
- Slow conversion to active compound
- Improved bioavailability and ease of administration
- Hydrolytically stable
- Model can be expanded to a wide array of PKC-binding scaffolds

Publications

- Jack L. Sloane1,‡, Nancy L. Benner1,‡, Katherine N. Keenan1,‡,†, Xiaoyu Zang1,‡, Mohamed S. A. Soliman3, Xiaomeng Wu3, Melanie Dimapasoc3, Matthew D. Marsden2, ‡,*, Jerome A. Zack2,3,*, and Paul A. Wender1,4,* "Prodrugs of PKC Modulators Show Enhanced HIV Latency Reversal and an Expanded Therapeutic Window" *Proc. Natl. Acad. Sci. USA* 2020 published May 5, 2020.
- Clayton Hardman1, Stephen Ho1, Akira Shimizu1, Quang Luu-Nguyen1, Jack L. Sloane1, Mohamed S. A. Soliman2, Matthew D. Marsden3*, Jerome A. Zack2,3*, Paul A. Wender1* "Design, Synthesis and Evaluation of PKC Modulators for Enhanced Cancer Immunotherapy" *Nat Commun* 11, 1879 (2020).

Patents

- Published Application: WO2018209062
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