Reversible Optothermal Isomerization of ProDrug Activity via Redshifted Photoabsorption and Heat Inactivation

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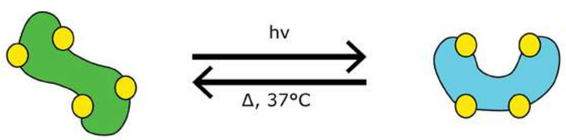
Background

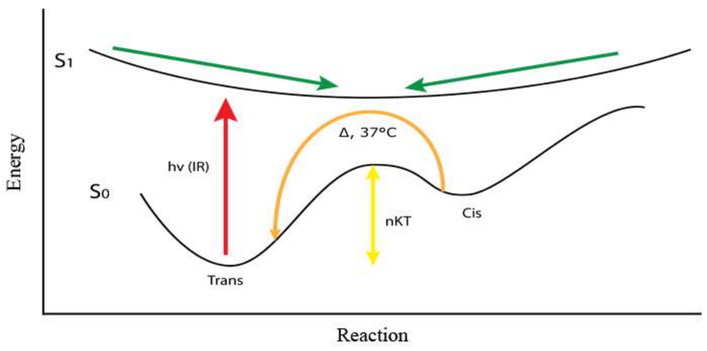
The **Cytotoxicity of drugs** poses a problem in treatments where strong dosage or potency is necessary, such as in chemotherapy. While certain drugs are effective, using a typical method of administration can result in collateral damage to a patient's body. Often, target cells or tissue are out of reach or surrounded by vulnerable areas, and lack of drug specificity can end up doing more harm than good. Pro-Drugs are a method of localizing drug delivery to bypass these problems.

The term "**prodrug**" refers to the sheathing of or the precursor to an intended drug. It is administered as an inactive chemical derivative of a pharmacological agent that gets converted into the active form of the drug through some chemical change. The intended application of prodrugs include controlling the absorption, distribution, and interaction of the active drug.

Enzyme-mediated catalysis of prodrugs still present problems with the minor biochemical differences between target and nontarget cells, often resulting in tocix side effects. **UV-photolysis** utilizes ultraviolet light in activating Prodrugs. Due to its high energy, UV light can damage many different cells and tissues, and often cannot penetrate deeply past the skin, restricting its utility. Both processes are **irreversible**, so once activated the compound cannot be deactivated.

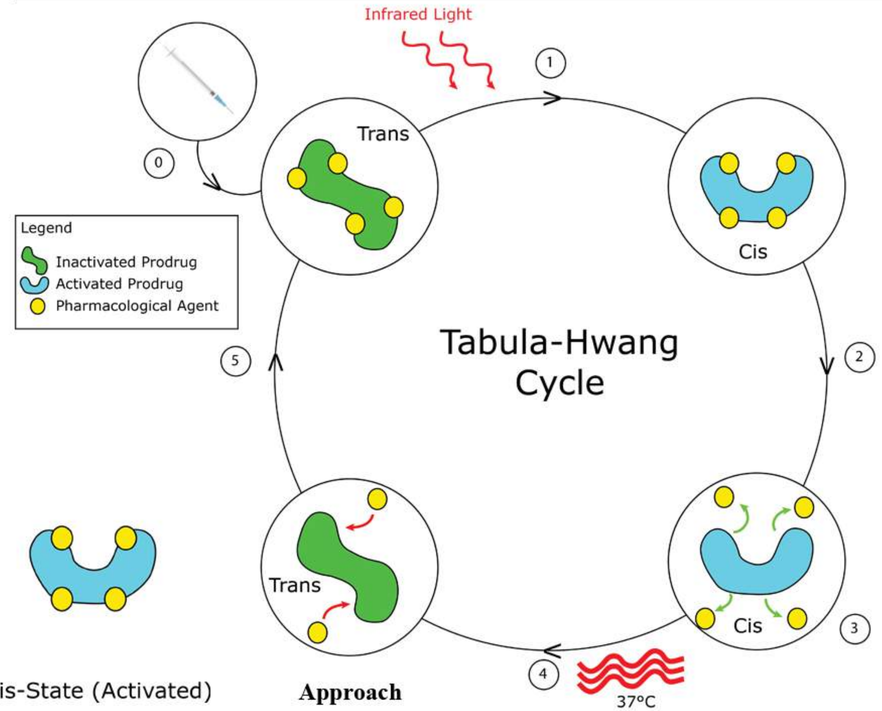


Trans-State (Inactivated) Cis-State (Activated)



Abstract

Prodrugs have proved to be an irreplaceable tool in the field of cancer therapy and other drug delivery platforms. Current methods for selective activation of prodrugs use UV Irradiation or enzyme-catalyzed cleavage. However, these systems have some major drawbacks. UV Irradiation is a potential mutagen and it doesn't penetrate deep enough – thus limiting the depth the drug can be placed as well as the exposure time. A general problem with enzyme-catalyzed cleavage still concerns the minor biochemical differences between target and nontarget cells, often resulting in toxic side effects. Furthermore, both these activation schemes are not reversible, thus limiting the range control the administrator has on the prodrug. We have developed a plan utilizing photochrome-inspired carriers to improve on current pro-drug design by enabling redshifted photoactivation and thermal inactivation, with eventual development for clinical application and commercial distribution. Our novel prodrug will combine information from mosses on how they absorb red-shifted light from the rainforest floor and utilize the reversible imsomerization properties of other photosensors. Successful integration of these properties would allow greater localization of pro-drug activity with lesser collateral damage at competitive costs.



Approach

- Distinguish compounds that have properties of red/infrared light-actiated trans-cis isomerization and head inactivated cis-trans thermal isomerization.

- Develop synthesis pathway and adapt use of selected caging compound for use as prodrug carrier.

- In vitro testing:
  a. Reproducible trials
  b. Seed prodrugs in 2D and 3D cultures
  c. Utilize various assays with controls to optimize pro-drug efficacy

- In vivo testing:
  a. Animal trials, Clinical trials
  b. New Drug Application (NDA) Approval

Steps
0. Injectable Administration of Inactivated ProDrug
1. Photoisomerization
2. Cleaving of ProDrug
3. Drug Delivery
4. Thermal Isomerization
5. Deactivation

Proof of Concept

Azo compounds, diarylethenes, and other similar chemicals are known to undergo trans to cis UV photoisomerization and cis to trans thermal isomerization through unique properties of their chemical structures.

Phytochromes harvested from moss were discovered to photoisomerize under redshifted light in the visible and infrared spectrum; synthesis pathways for these compounds have also been discovered.

By combining the properties of the two into a carrier, it is then possible to create a prodrug that is inactive when attached to said carrier, photolysed and released under low energy light, and rebound and deactivated when not under light stimulus.

Predicted Results

- In vitro: Modified prodrug shows greater localization response with redshifted photoactivation; analytical confirmation of cis-trans isomerization of carrier and subsequent inactivation of drug.

- In vivo: Improved prodrug shows a reduction/elimination of adverse side effects in test subjects, greater penetration depth of stimulation over UV-photolytic prodrugs; precise control over localization zone of drug delivery

Extended Studies

- Further optimization of delivery localization and simplificaion of carrier will result in faster manufacturing and less cost in future iterations.

- Adaptation of successful carrier compound to multiple drugs could increase efficacy of prodrug use across more medical applications with less adverse side effects.

- Devise accurate logarithm for drug inactivation rate with respect to several variables.

- Identify optimal penetration depth for future reference.

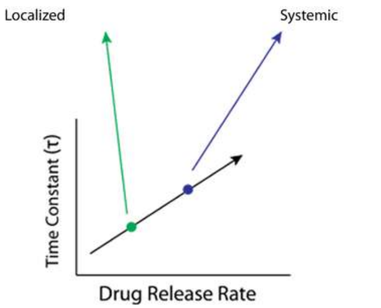
- Determine limits on reversible isomerization.

Specific aims

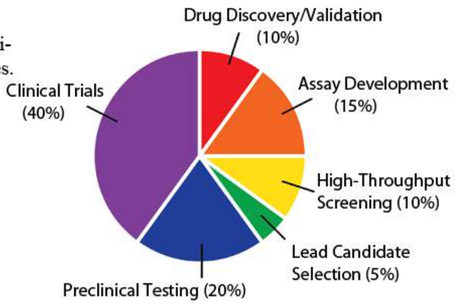
- Identify and synthesize compounds with trans-cis photoisomerization under red/infrared light and cis-trans thermal isomerization at 37°C.

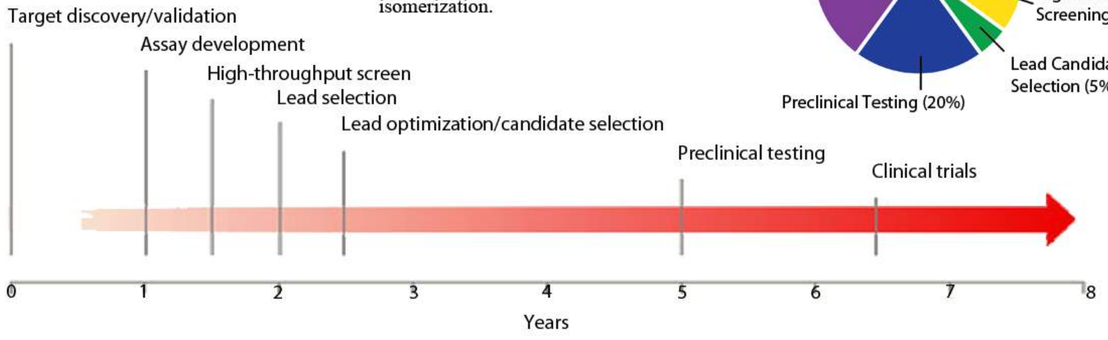
- Adapt compound into carrier for prodrug retaining these properties with binding inactivation.

- Conduct in vitro and in vivo trials of modified prodrug to confirm improvement.



Predicted Allocation of Funds





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