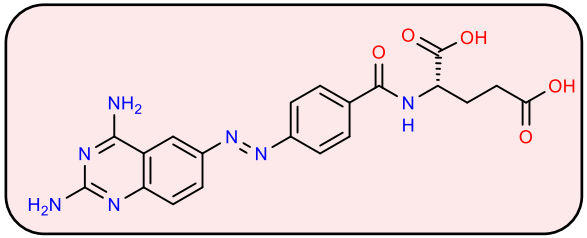
Phototrexate

Photopharmacological Chemotherapy:

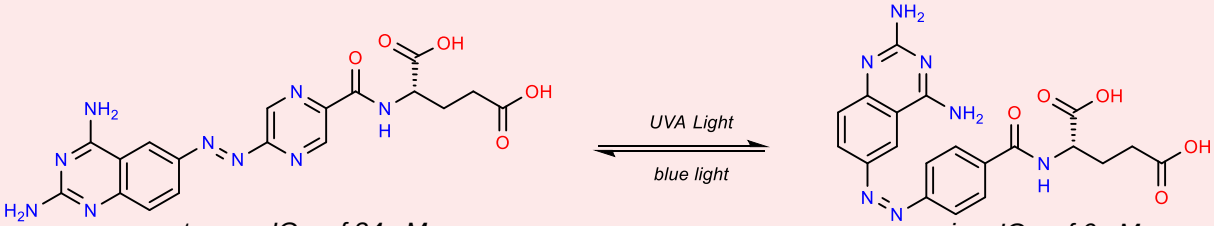


phototrexate

*Phototrexate was developed in 2018 as the first photoswitchable inhiboitor of dihydrofolate reductase (DHFR), acting as a photochromic analogue of methotrexate, a widely prescribed chemotherapeutic for cancer and psoriasis.
*The molecule exists in its thermodynamically preferred trans conformation which exhibits low cytotoxicity and can be irradiated with UVA light to convert to its cis form, which demonstrates potent anticancer activity, inhibiting DHFR.
*Demonstrates proof-of-concept for light-regulated cytotoxic small molecules, providing a platform which could allow for more selective, less dangerous, and more efficient methods of anti-cancer treatment.

Mode of Activation:

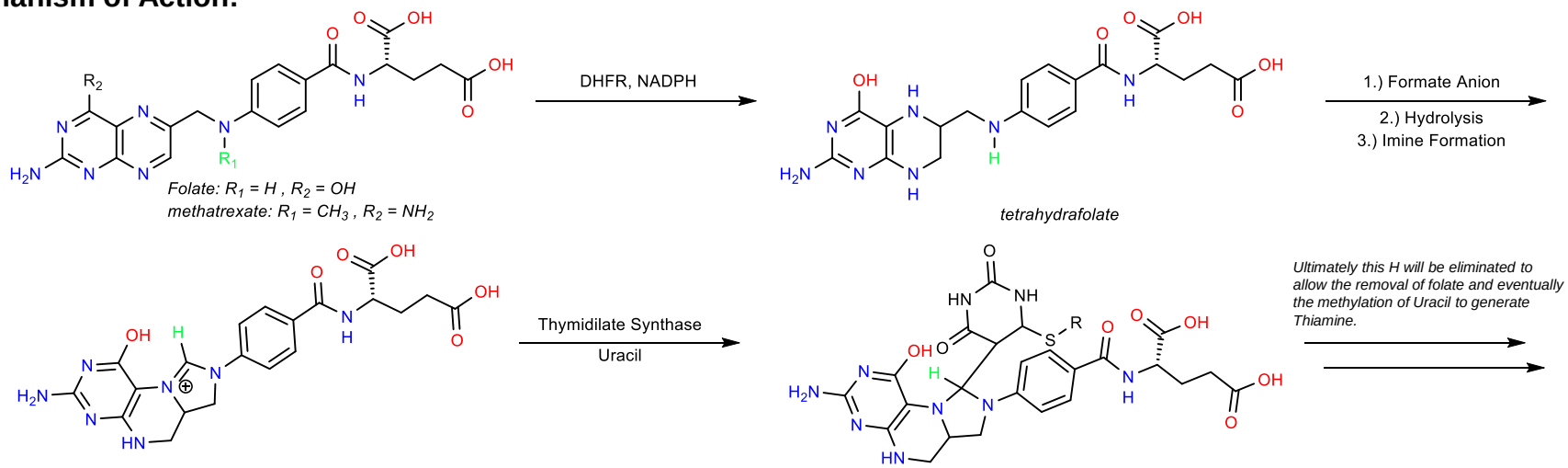
*Circumvents many problems of conventional chemotherapeutics.
- -Allows higher therapeutic index
- -Allows high specificity
- -Minimal off-target cytotoxicity
- -Allows high spatiotemporal control, thus allowing higher safe drug dosages



trans – IC_{50} of 34 μM

cis – IC_{50} of 6 nM

Mechanism of Action:



Folate: R_1 = H , R_2 = OH
methatrexate: R_1 = CH_3 , R_2 = NH_2

tetrahydrafolate

Similarly, phototrexate lacks this key H. Thus, it will become bound to DHFR and will not be eliminated, preventing thiamine synthesis., essential for translation.

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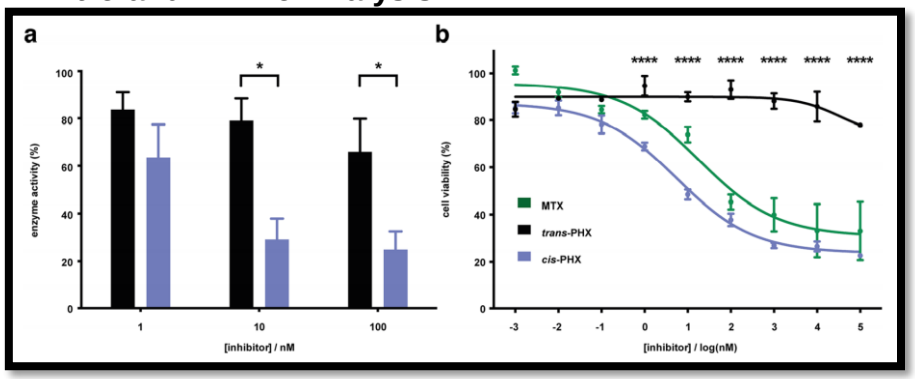
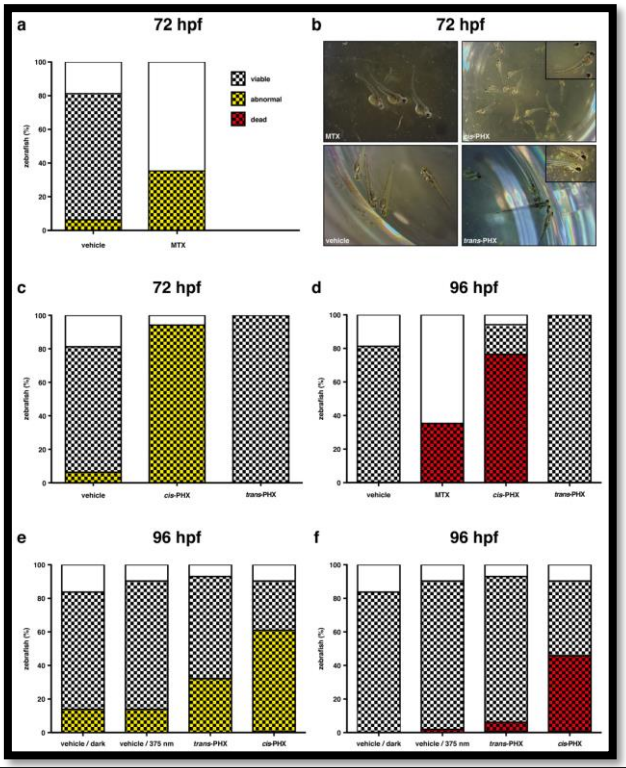
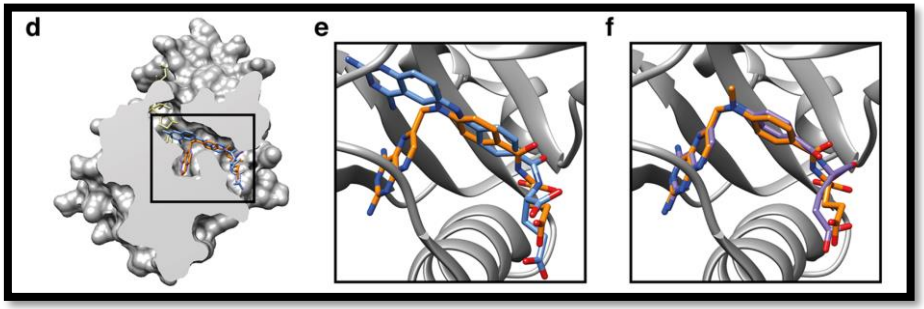
Phototrexate

In vitro and *in vivo* Analysis:



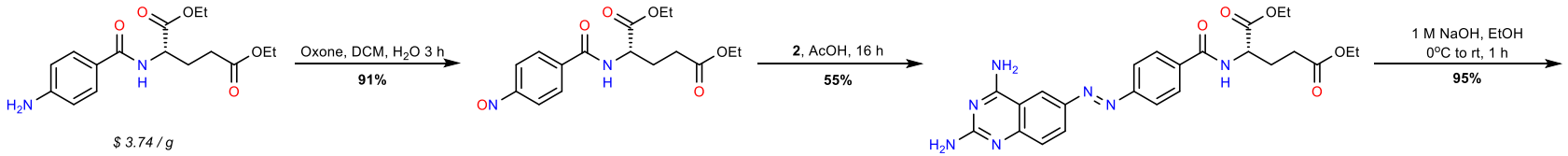
hpf = *hours post fertilization*





d – *methotrexate*
e – *trans phototrexate*
f – *cis phototrexate*

Synthesis:



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