

Medicinal Chemistry 562 - Rettie Problem Set 1

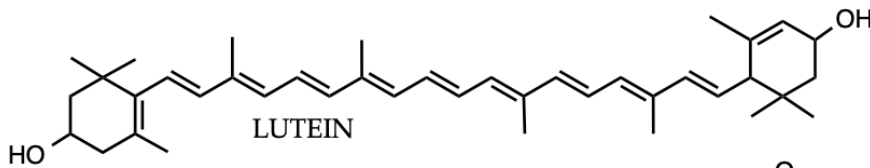
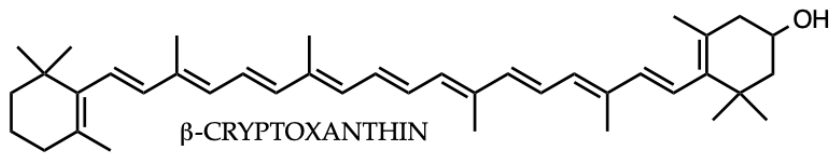
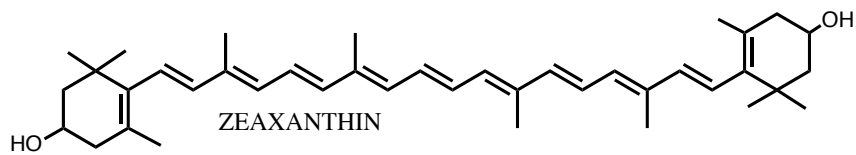
1. List three important differences of physiological consequence between the fat-soluble and water-soluble vitamins.

Slower onset for deficiency state

More likely to cause toxicity

Do not act as cofactors for energy-producing reactions

2. Answer questions a. and b. for each the two carotenoids shown below.



- a. Can these carotenoids yield retinal following BCMO metabolism? If so, how many equivalents of retinal are theoretically possible?

Zeaxanthin yields 0, β -cryptoxanthin yields 1, Lutein yields 0

- b. Lutein and zeaxanthin were constituents of the AREDS2 eye-drop formulation for treating acute acular degeneration. What was the rationale for using them?

While neither carotenoid yields retinal, both are antioxidants, which is the rationale for the inclusion in AREDS2.

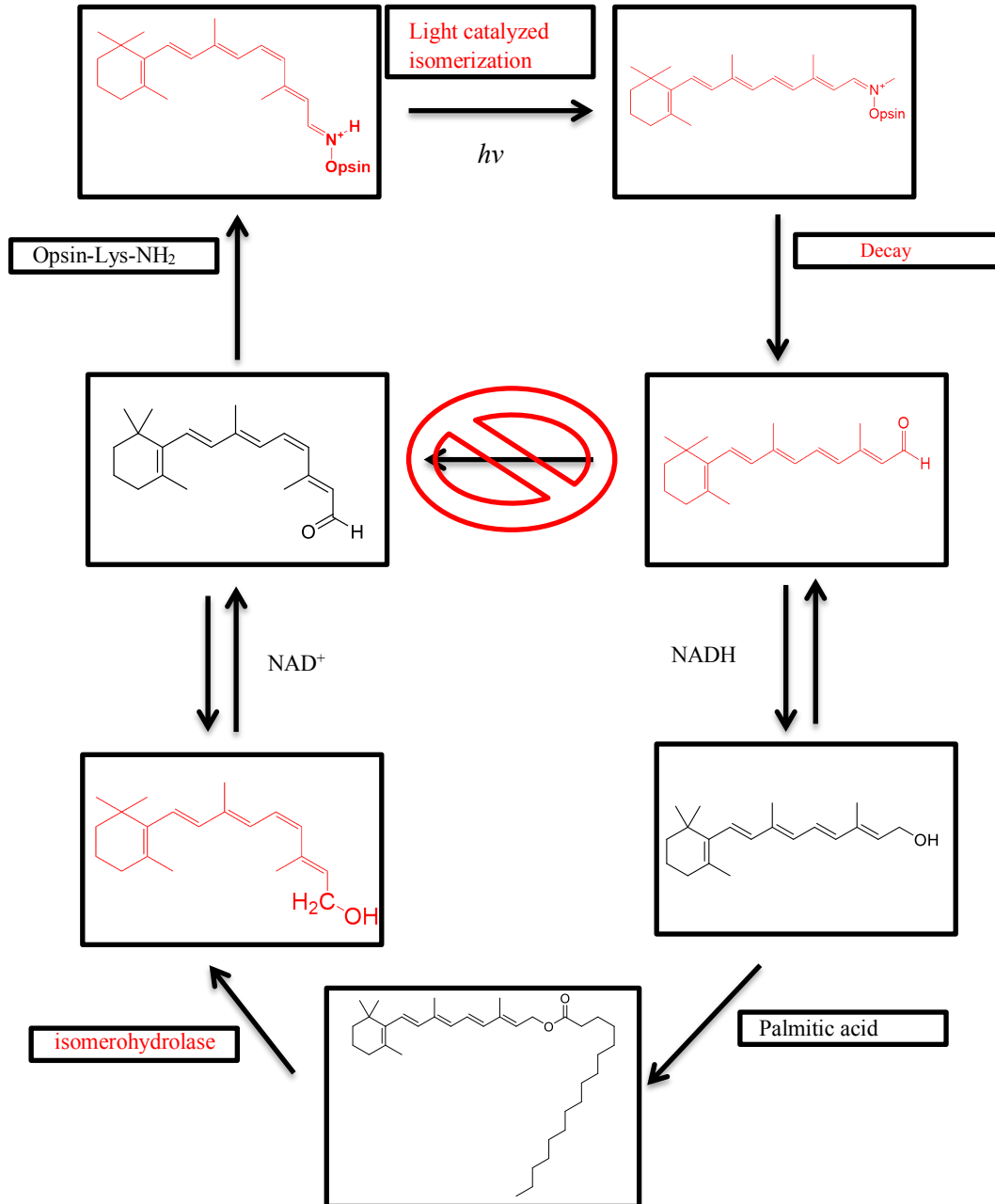
3. What 3 basic functions do the active forms of vitamin A support? Briefly discuss the effect of vitamin A deficiency with regard to these basic functions.

Vision: Xerophthalmia, keratinization of cornea leads to ulceration and eventual blindness.

Growth/Development: Sub/super normal intake can cause weak bones as well as low mucin synthesis and high keratin synthesis (hyperkeratosis) causes skin fissures that can lead to infection.

Immunity: Changes to mucosal surfaces, impaired antibody responses, changes in lymphocyte subpopulations, altered T-cell and B-cell function

4. Fill in the blanks on the rhodopsin cycle.



5. What is a RAMBA? What condition might it be used to treat? Which enzyme does it inhibit?

A RAMBA is a retinoic acid metabolism-blocking agent.

Can be used to treat the skin disease, lamellar ichthyosis, by blocking CYP26, thereby increasing retinoic acid levels to promote cellular proliferation and differentiation.

6. Case study: A 44-year-old man presented with a 3-year history of intermittent night blindness. He suffered from short bowel syndrome due to ileocecal resection in Crohn disease. His serum vitamin A level was measured at 0.11 ug/ml. Oral vitamin A supplementation was ineffective, but subsequent treatment with a liposoluble infusion containing vitamins A, D, E and K once daily for 3 days resolved these visual problems.
Provide a detailed analysis of this case explaining what all the data provided are telling you.

Night blindness is an early sign of vitamin A deficiency. Serum vitamin A is below 0.3 microgram/ml confirming deficiency, possibly as a consequence of the bowel resection that likely affects bile acid homeostasis and causes malabsorption of fat-soluble vitamins. This is consistent with the lack of effect of oral treatment but resolution of the problem after delivering vitamin A by infusion.

7. Retinoids are administered orally for the treatment of acne and other skin conditions. Are there risks associated with this kind of treatment? If so, discuss briefly.

Yes, oral retinoids are teratogenic.

8. Explain fully why the 2nd generation retinoid Etretinate was removed from the market.

Etretinate was an ester prodrug for the active acid, acitretin. However, etretinate had a very long half-life of 3-4 months. Since it takes 5 half-lives to reduce drug concentration by >97% there was a risk of birth defects for women of child-bearing age that persisted for ~18 months. This made treatment with etretinate very challenging in this patient population. Since it was a prodrug, the obvious 'solution' was to remove etretinate and replace it with acitretin, which has a much shorter half-life of only a few days. This was thought to make treatment more manageable.

9. Identify specific ligands for RXR and RAR.

RAR- most retinoids including all trans retinoic acid.

RXR – 13 cis retinoic acid and bexarotene.

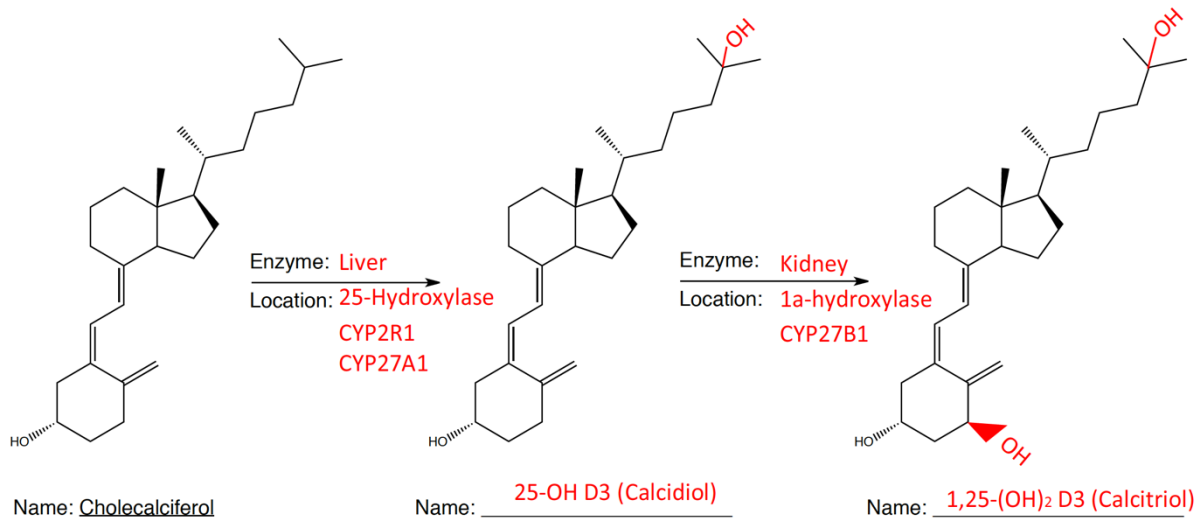
10. Explain why 1 microgram of all-trans retinol is equivalent to 2 micrograms of all-trans β -carotene in oil.

1 ug retinol is equivalent to 2 ug of beta-carotene in oil (a highly absorbable formulation) because the BCMO enzyme in the intestine is not 100% efficient.

11. Why should consumers (especially smokers and past smokers) avoid β -carotene as a single dietary supplement?

Because supplementation with beta-carotene resulted in an *increased* risk of lung cancer in clinical studies.

12. Cholecalciferol is the structure on the far left. Which fat-soluble vitamin is this? **Vitamin D3**



- a. Cholecalciferol is hydroxylated twice by P450s to yield the active form of this vitamin.
- Draw in the hydroxyl groups on the structures provided
 - Indicate which CYP carries out each hydroxylation and the tissue location where it takes place in.
 - Finally, name each molecule (there are multiple names for each!).

13. Vitamin D and parathyroid hormone (PTH) have important roles in metabolic bone disease.

a. Metabolic bone disease typically happens as a result of failure in which organ?

Kidney

b. Metabolic bone disease is associated with deficiency of which mineral?

Calcium

c. Describe how PTH interacts with bone, the failed organ in “part a”, and the mineral in “part b”.

PTH release causes calcium resorption from bone when serum calcium levels are too low. PTH works in concert with vitamin D to increase kidney reabsorption of calcium and increase renal synthesis of activated vitamin D via CYP27B1. (There are also effects in the gut to increase calcium absorption there).

14. Complete the table.

Vitamin	Function / Uses	Deficiency States	Toxicities	Daily Value	Upper Limit
A	<p>Vision, growth and development, Immunity.</p> <p>-Cofactor for opsin -Ligand for RXR and RAR</p>	<p>-Night blindness -Xerophthalmia -Dry rough skin -Decreased resistance to infection -Faulty teeth development and slower bone growth.</p>	<p>-Hypervitaminosis -Yellowing of skin -Teratogenic (not if topical)</p>	<p>5,000 IU/day</p>	<p>10,000 IU/day</p>
D	<p>-Maintain serum calcium and phosphate concentrations.</p>	<p>-Rickets -Osteomalacia</p>	<p>-Calcification of soft tissues such as the lung and kidney.</p>	<p>400 IU/day</p>	<p>4,000 IU/day</p>