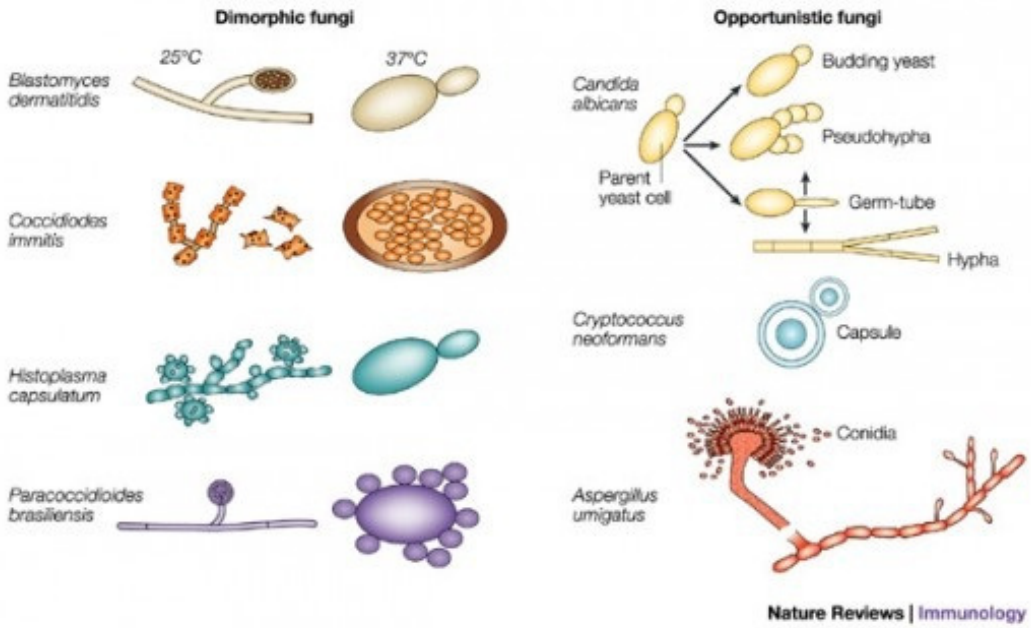
Antifungals



only ~100 of the thousands out there can infect humans

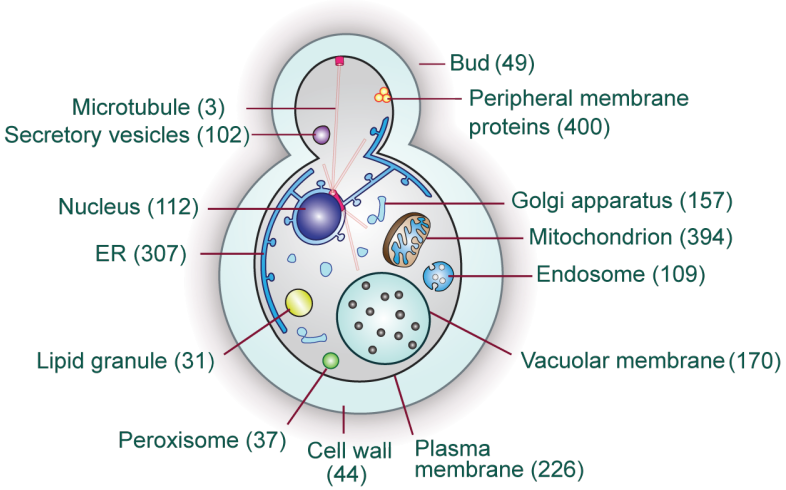
molds or yeast

molds → multicellular aggregate

yeast → colonies of single cells

mycotic infections

- Superficial
  - tinea pedis
  - Corporus rubrum
- Subcutaneous or deep



fungal cell wall

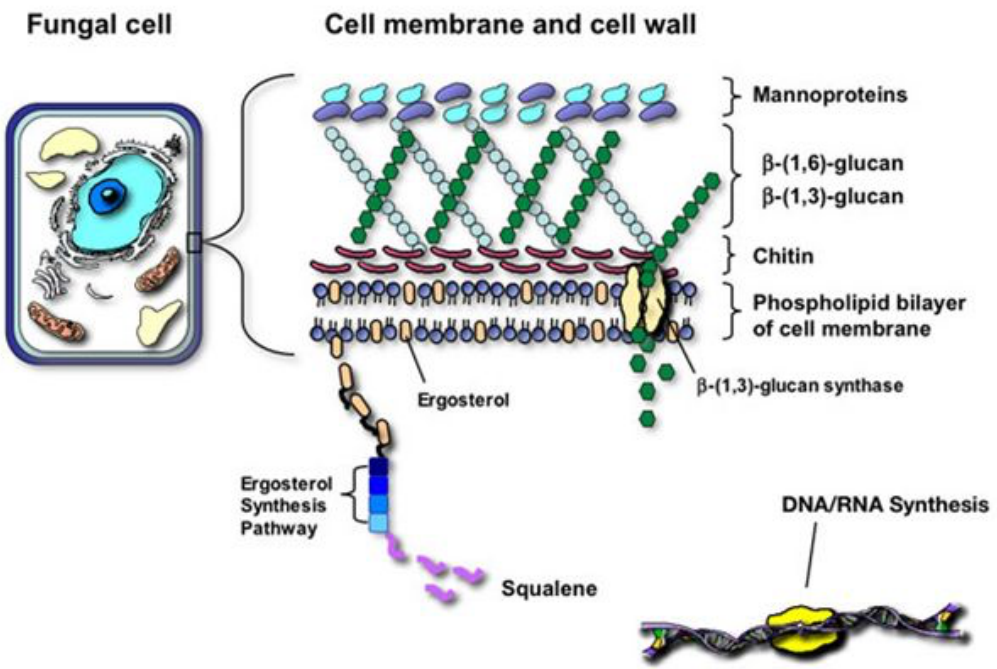
structure + metabolism

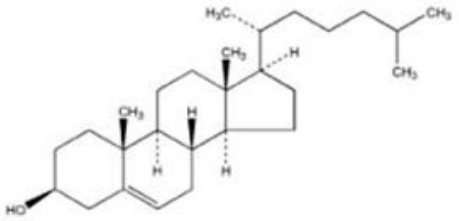
to ours

hard to find good

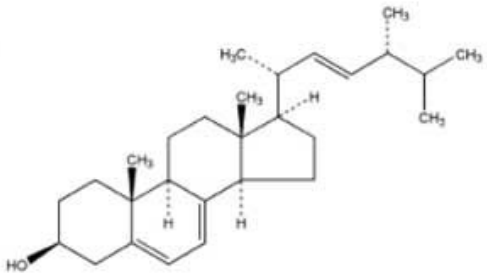
targets for drugs

Fungal Plasma Membrane





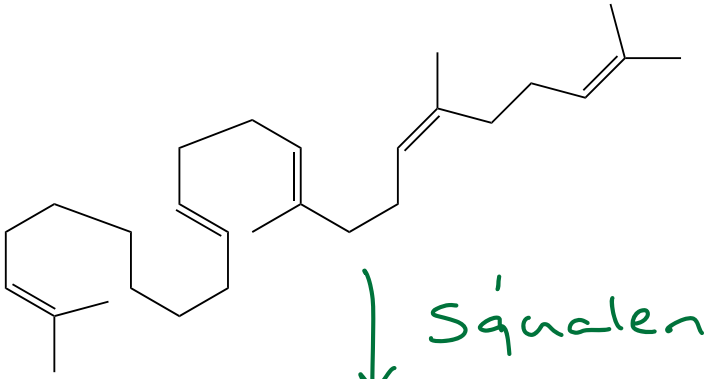
Cholesterol



Ergosterol

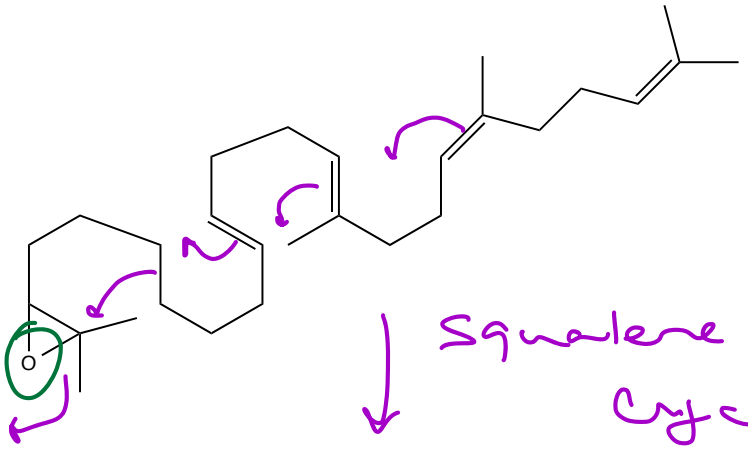
1) they use ergosterol instead of Cholesterol in membranes

2) cell wall

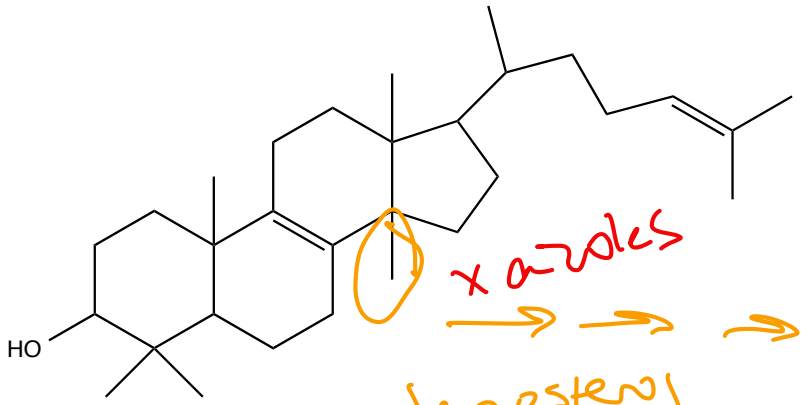


Squalene

↓ squalene epoxidase (X allyl amines)

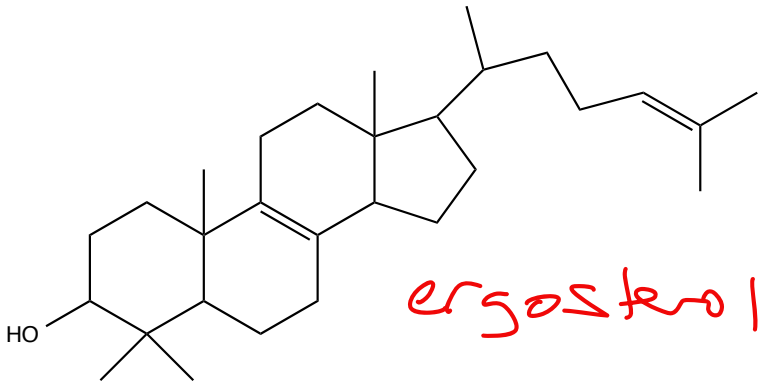


↓ squalene epoxide cyclase



lanosterol

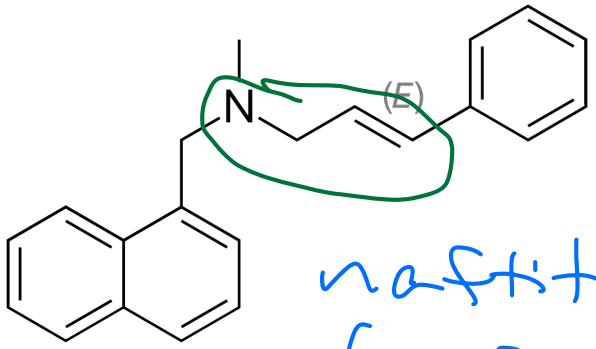
X azoles → → → → → lanosterol 14α demethylase



ergosterol

Allylamines

derived from 3-aminopropene

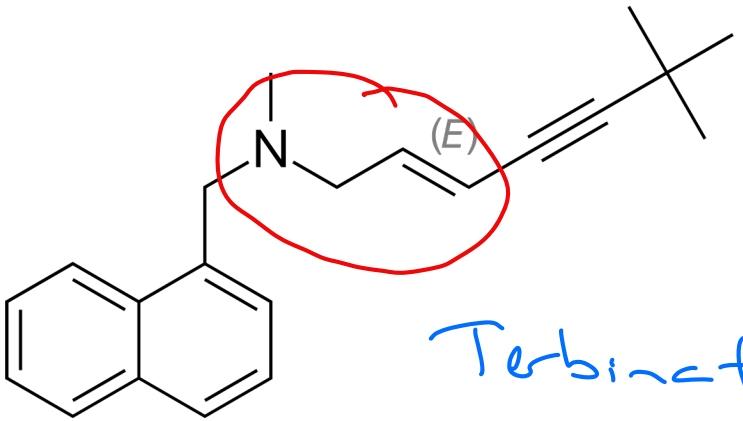


naftitine
(naftin)

- used as surface antifungal skin + nails
- extensive first pass metabolism

occurs before drug enters systemic circulation

- decreases ergosterol
  transport proteins don't work well
- increases [squalene] which is toxic to fungi



Terbinafine

Lamisil

- taken orally or topically

Antifungals often have drug-drug interactions

w/ this one Cimetidine

inhibits an enzyme that metabolizes Terbinafine

Codeine, desipramine

Azole Antifungals

α14 demethylase inhibitors

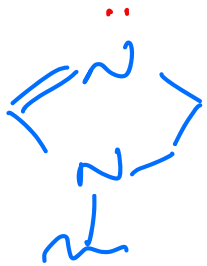
is a Cytp450 enzyme

it has a heme

w/ an Fe

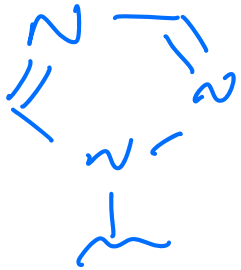
2 Classes

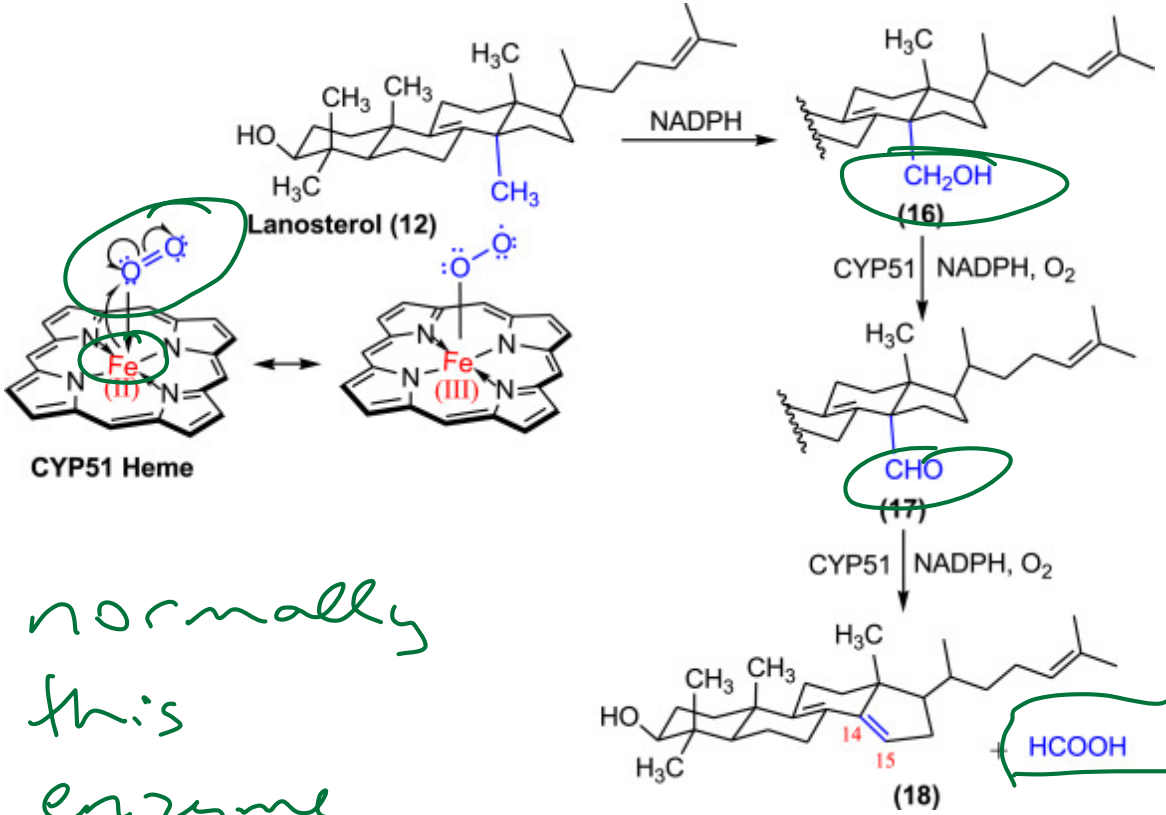
Imidazoles



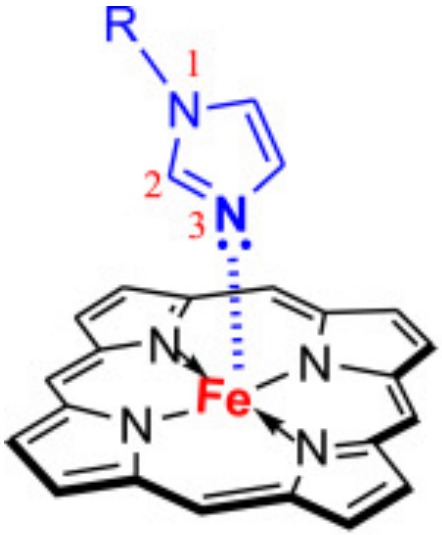
these coordinate + block the Fe

Triazoles

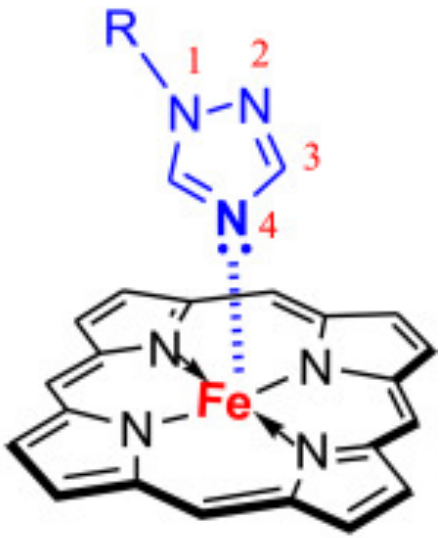




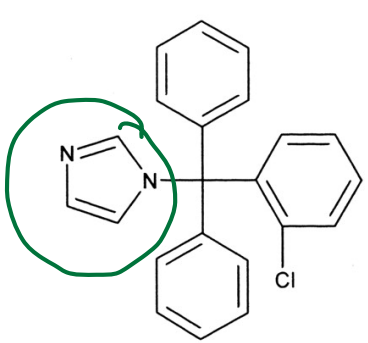
normally this enzyme does an oxidative demethylation



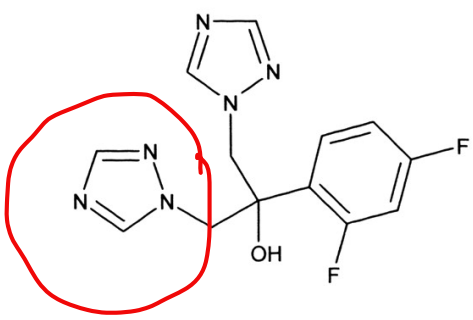
CYP51 Heme



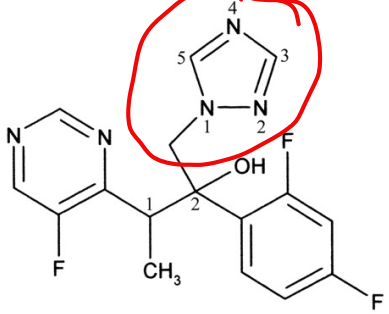
CYP51 Heme



Clotrimazole



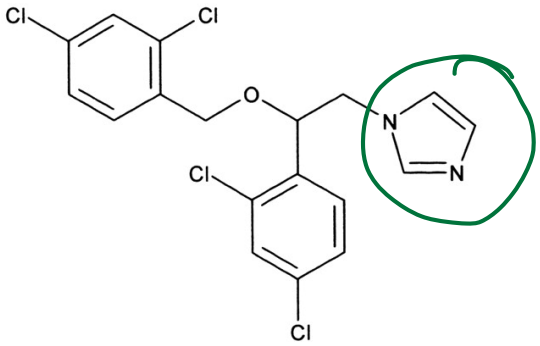
Fluconazole



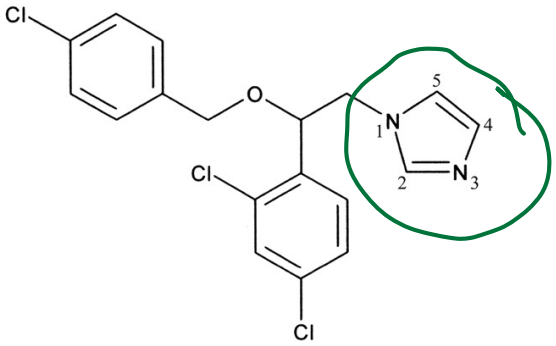
Voriconazole

Imidazole

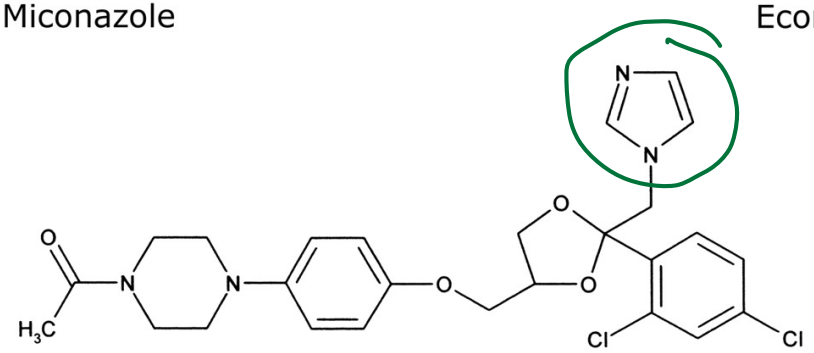
Triazole



Miconazole

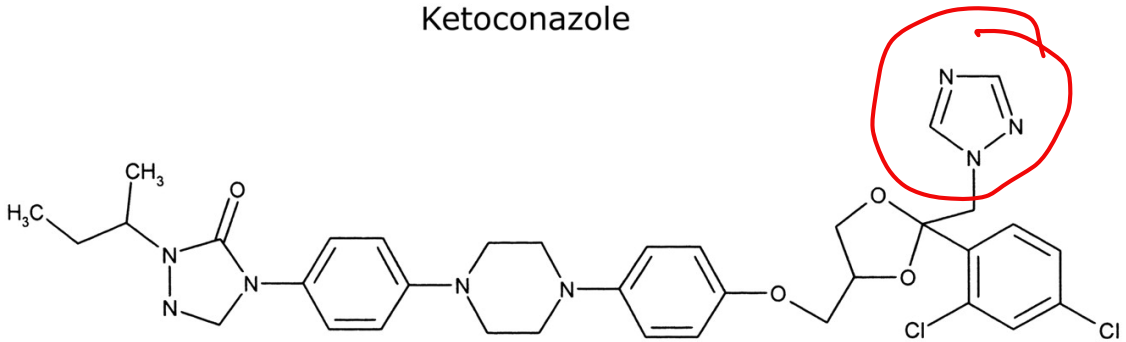


Econazole



Ketoconazole

first one that was orally available



Itraconazole

can lower levels of testosterone + cortisol

Fluconazole

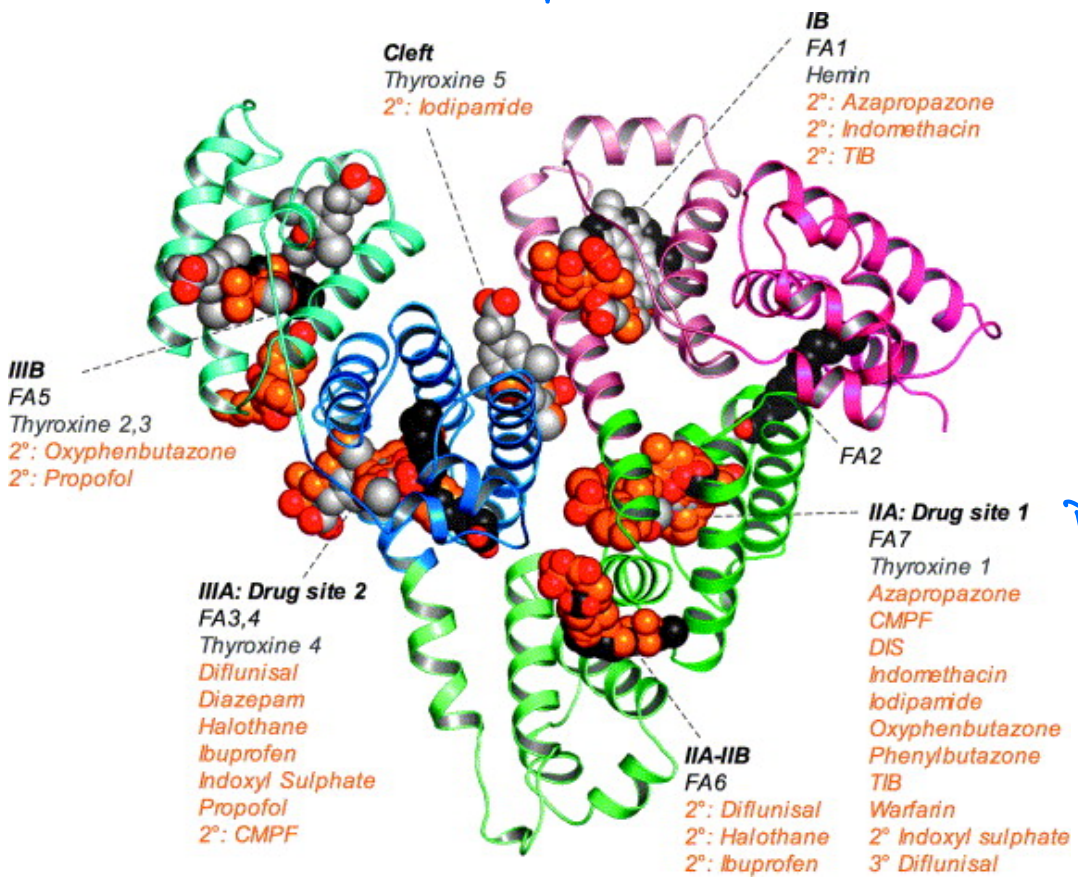
- alopecia
- drug drug interactions

- almost 100% bioavailable
  no first pass metabolism

* also an inhibitor for Cyp 2C9

Warfarin is metabolised by this one

Side Effects part I



Serum albumin

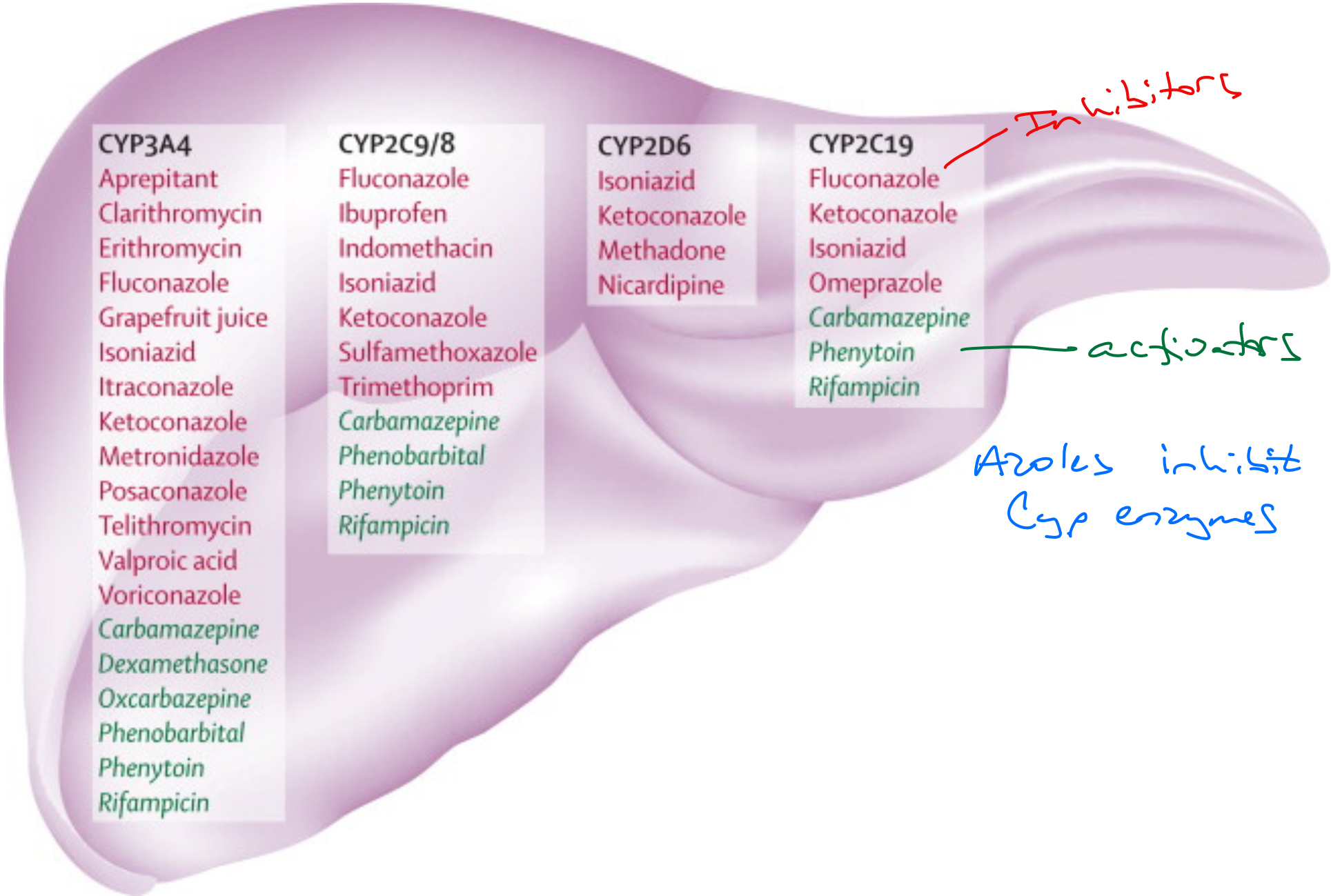
Drugs bind proteins in blood + get carried around

Drugs can displace one another

- change $[Drug]_{blood}$

* patients who are malnourished may have less

Side effects part 2



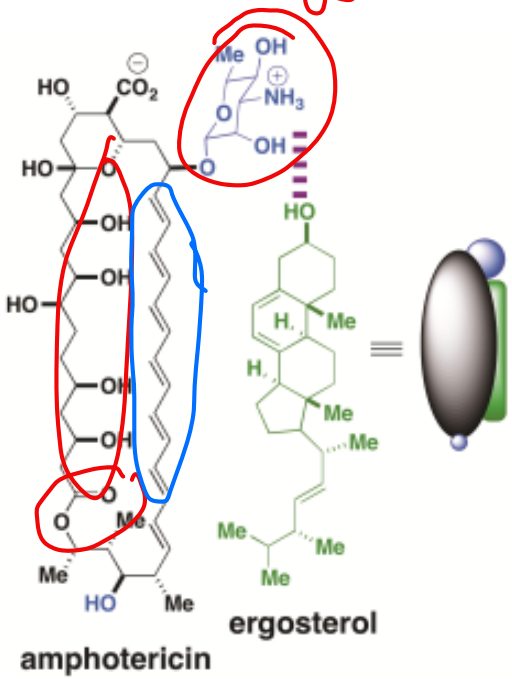
Polyenes

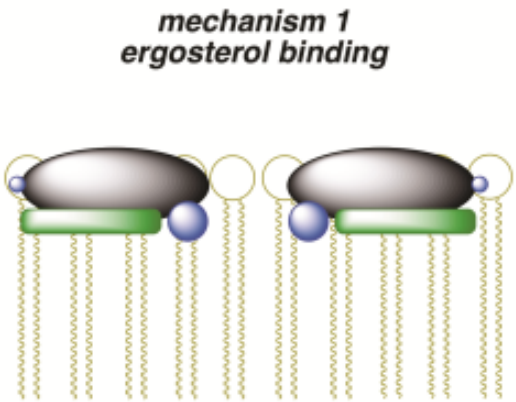
macrocyclic ketones

all have a hydrophilic region w/ several –OH's

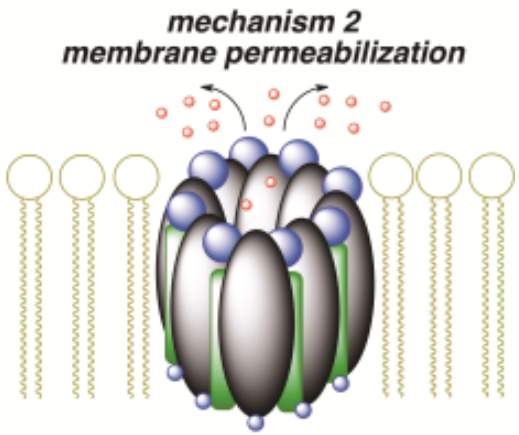
usually a sugar

Lipophilic region lots of = more = 's works better

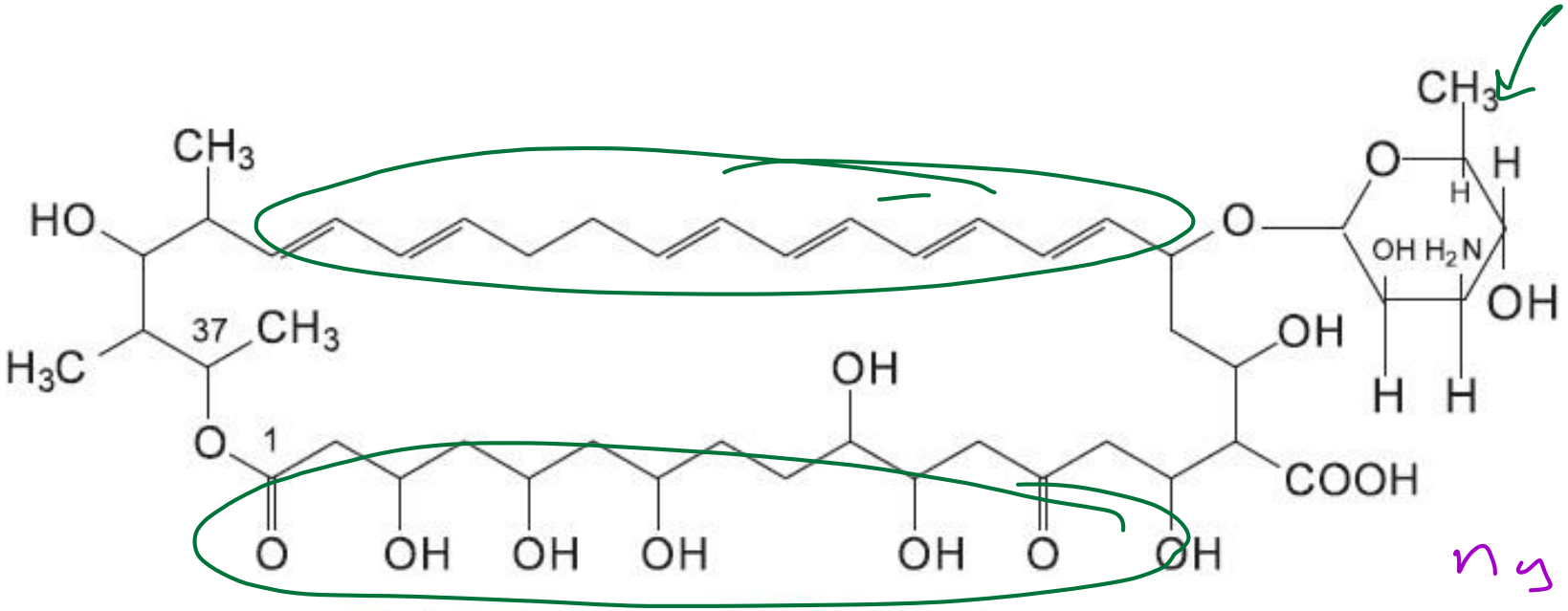




associate with ergosterol



forms pores through membranes



$C_{47}H_{75}NO_{17}$ MW 926.13

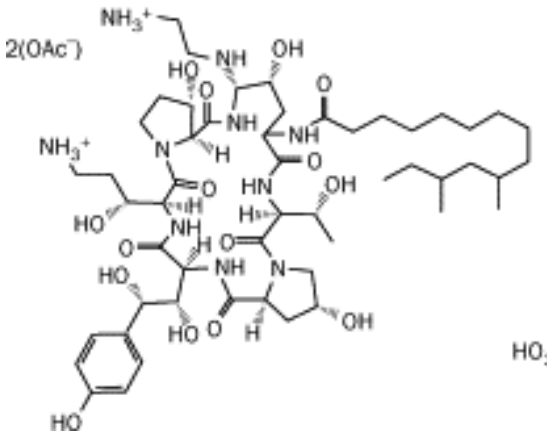
nystatin

Echinocandins

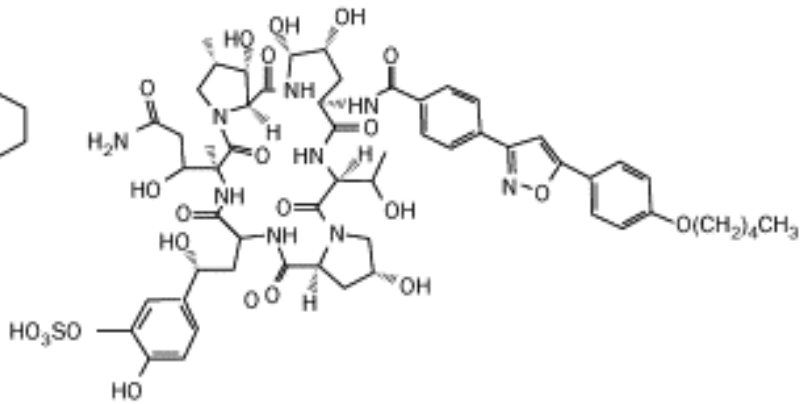
target the cell wall structure
act as inhibitors for the enzyme that makes glucan crosslinks

- low ~~toxicity~~
- few side effects
- not absorbed well, used by IV

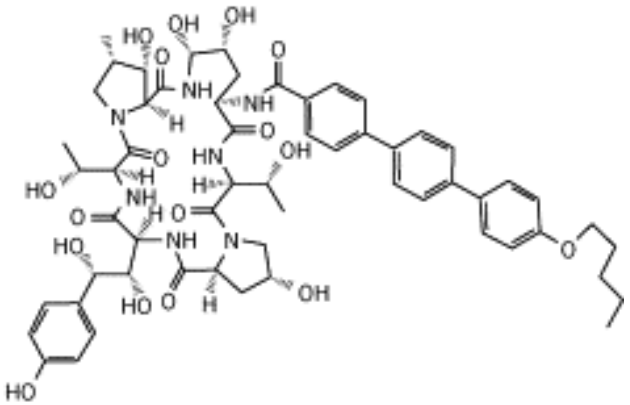
Caspofungin



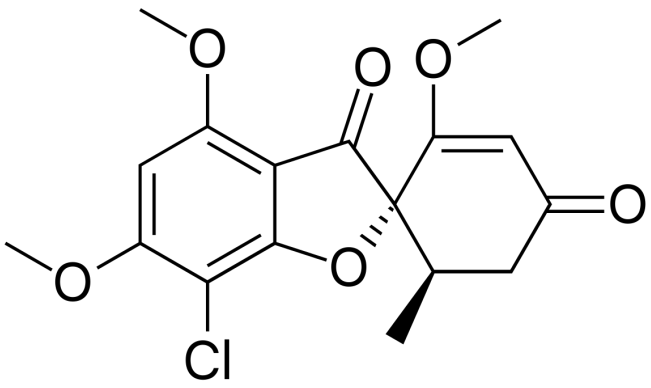
Micafungin



Anidulafungin



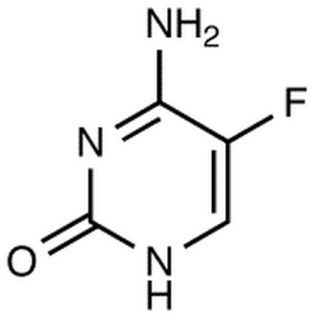
Griseofulvin



Binds tubulin
interferes with
microtubule formation
→ inhibits cell division

used for nail infections

Flucytosine

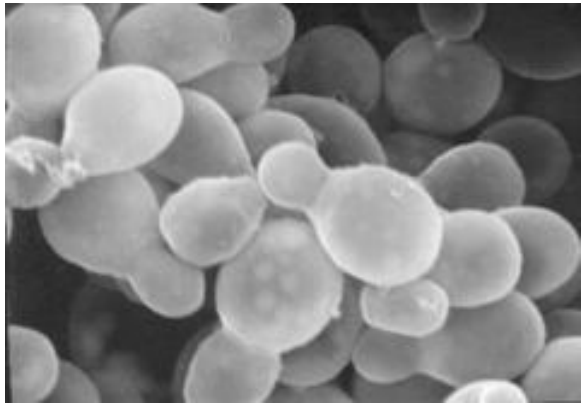


Inhibits

thymidylate synthase

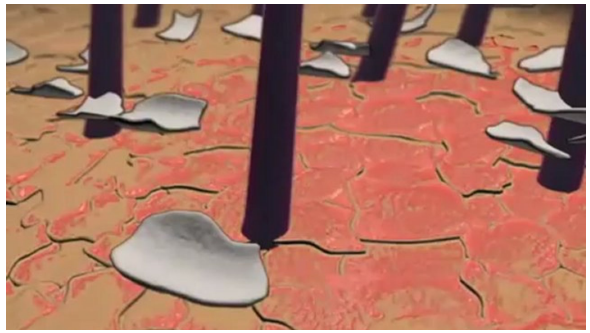
– inhibits replication

an antimetabolite



nizoral = Ketoconazole

Selenium sulfide = Selsun Blue

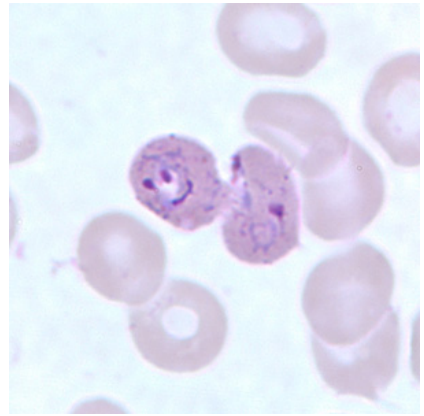


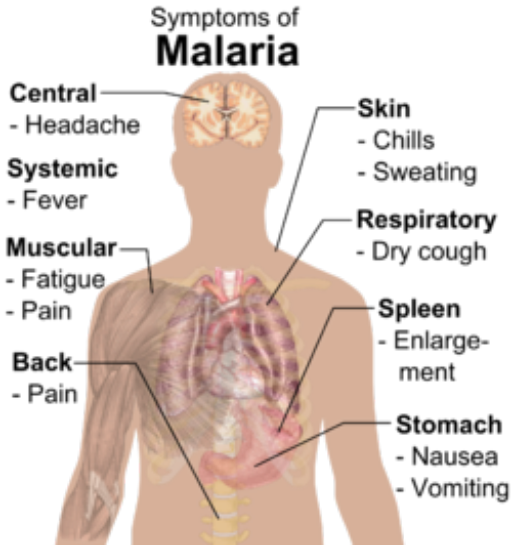
ter- T-gel

P. ovale

Pityosporum ovale

- normally found on skin





P. ovale

Plasmodium