



“Where’s the Fun in Fungus?”
An Introduction to the Antifungal Space

Literature Talk

February 13th, 2024

Iona Mathis McWhinnie

MacMillan Group

Princeton University

Another Public Health Crisis?

BARDA makes support available for development of novel antifungals to boost national preparedness

WEB ANNOUNCEMENT

SHARE    



BARDA is seeking private sector partners who are developing late-stage, broad-spectrum, next-generation antifungal drugs to treat high-priority fungal infections. Patients affected by any mass casualty emergency, such as a chemical, biological, radiological, or nuclear (CBRN) incident, pandemic influenza, and other emerging infectious diseases, are at an increased risk of developing a secondary fungal infection, which can contribute to increased morbidity and mortality and prolong patient recovery.

Congress Reintroduces the Pasteur Act

May 1, 2023

John Parkinson

Article



Members of both branches brought it back to gain support and passage of a bill aimed at greater development of antibiotics.

"The PASTEUR Act brings together the public and private sectors to address these drug development market failures, increase public health preparedness, and help usher in a new era of antibiotic development," said Ferguson in a statement. "This essential legislation will also improve appropriate antibiotic use across the healthcare system while enhancing and safeguarding new antibiotic development. Simply put, we must act now to keep research and development from falling behind."

Increasing Threat of Spread of Antimicrobial-resistant Fungus in Healthcare Facilities

Press Release

For Immediate Release: Monday, March 20, 2023

Contact: [Media Relations](#)

(404) 639-3286

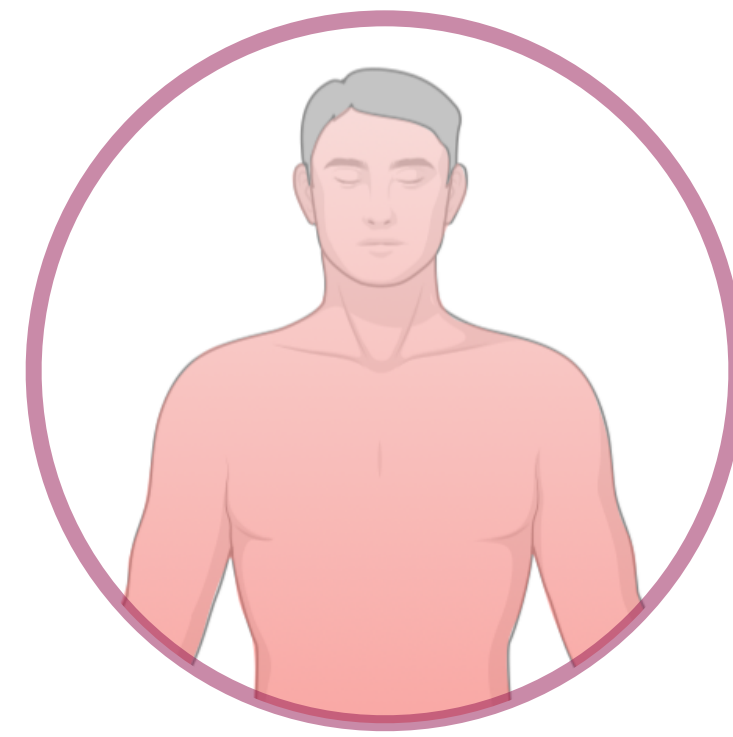
Candida auris (*C. auris*), an emerging fungus considered an urgent antimicrobial resistance (AR) threat, spread at an alarming rate in U.S. healthcare facilities in 2020-2021, according to data from the Centers for Disease Control and Prevention (CDC) published in the *Annals of Internal Medicine*. Equally concerning was a tripling in 2021 of the number of cases that were resistant to echinocandins, the antifungal medicine most recommended for treatment of *C. auris* infections. In general, *C. auris* is not a threat to healthy people. People who are very sick, have invasive medical devices, or have long or frequent stays in healthcare facilities are at increased risk for acquiring *C. auris*. CDC has deemed *C. auris* as an urgent AR threat, because it is often resistant to multiple antifungal drugs, spreads easily in healthcare facilities, and can cause severe infections with high death rates.

WHO releases first-ever list of health-threatening fungi

25 October 2022 | Departmental news | Reading time: 3 min (715 words)

WHO today published a report highlighting the first-ever list of fungal "priority pathogens" – a catalogue of the 19 fungi that represent the greatest threat to public health. The WHO fungal priority pathogens list (FPPL) is the first global effort to systematically prioritize fungal pathogens, considering the unmet research and development (R&D) needs and the perceived public health importance. The WHO FPPL aims to focus and drive further research and policy interventions to strengthen the global response to fungal infections and antifungal resistance.

Invasive Fungal Infections

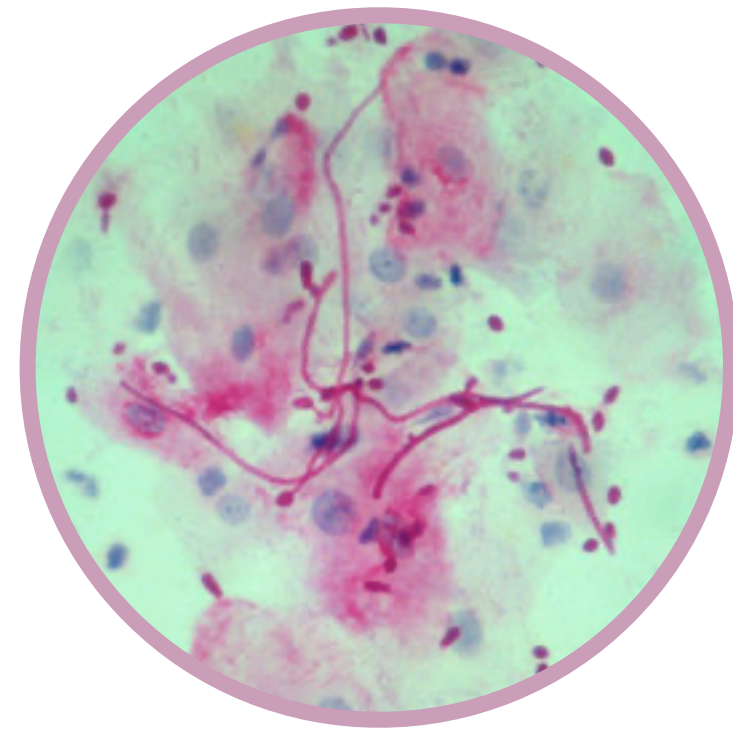


Immunosuppression
3% US Population
90% invasive fungal infections

Invasive Fungal Infections



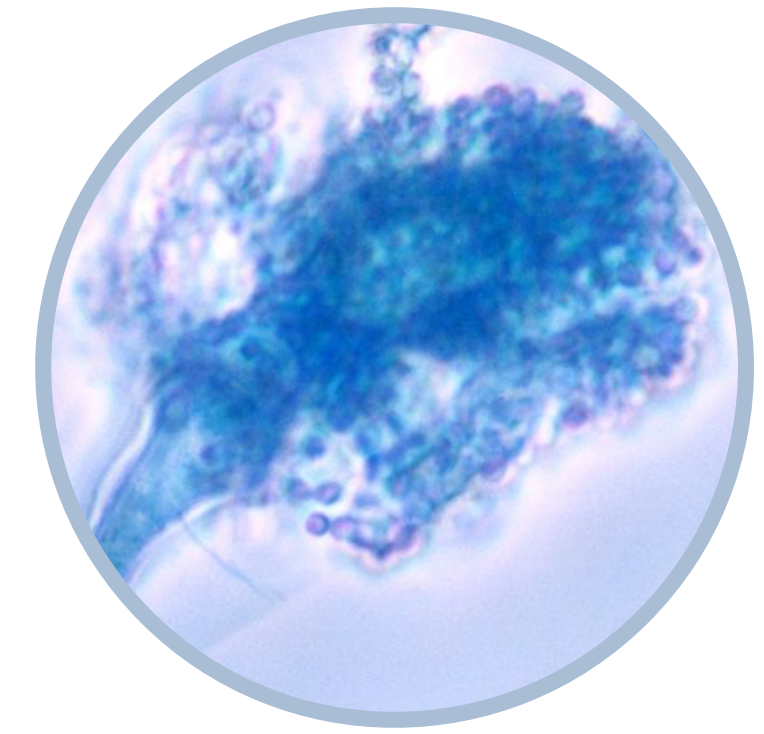
Immunosuppression
3% US Population
90% invasive fungal infections



Candidiasis
>400k worldwide
46-75% mortality



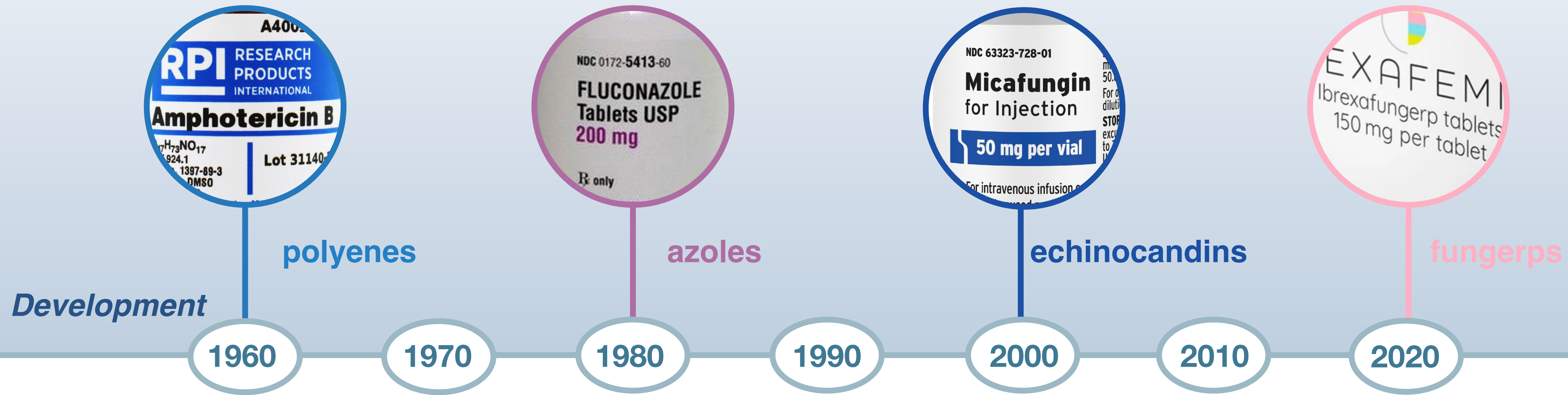
Aspergillosis
>200k worldwide
30-95% mortality



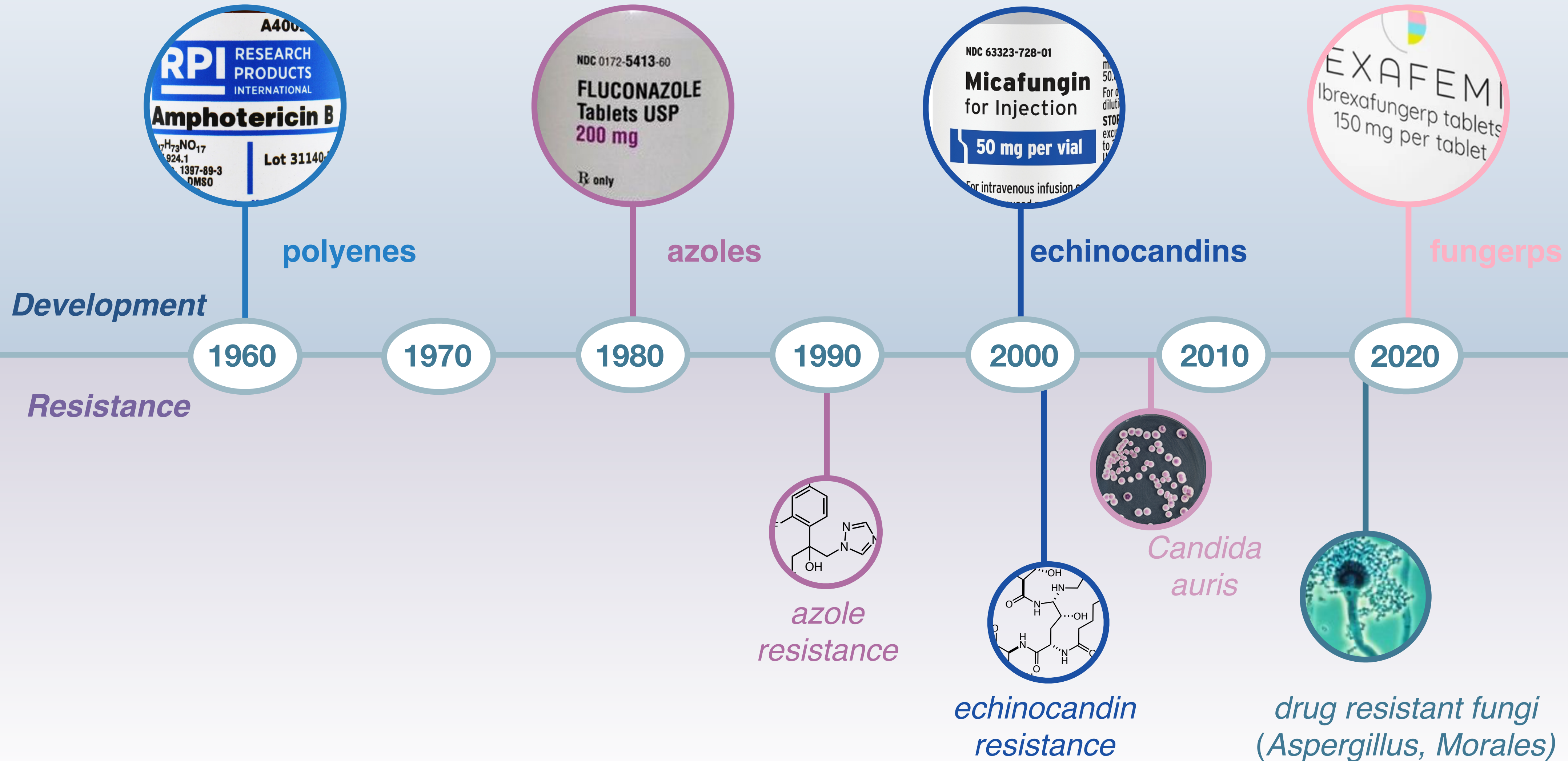
Rare Molds
20-30k worldwide
30-90% mortality

\$3.8 billion market and high unmet need

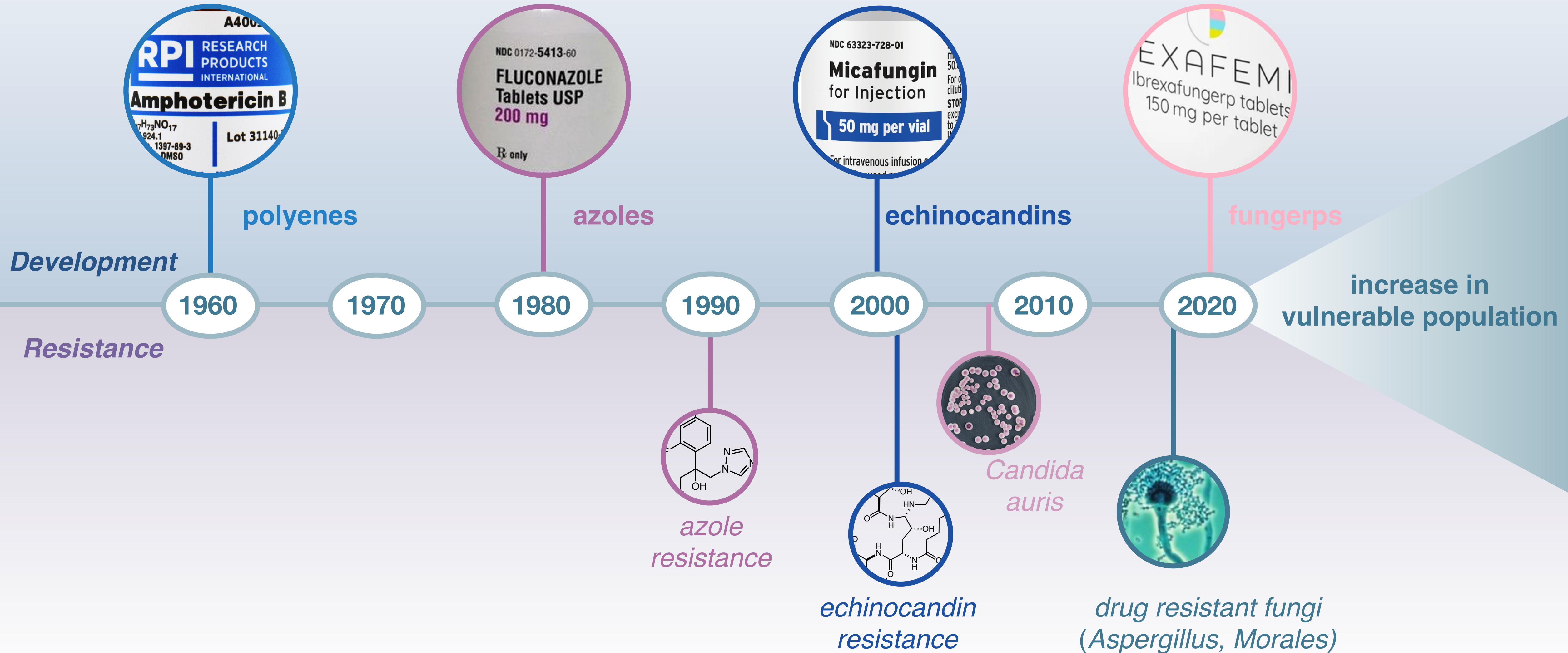
Antifungal Development and Resistance



Antifungal Development and Resistance



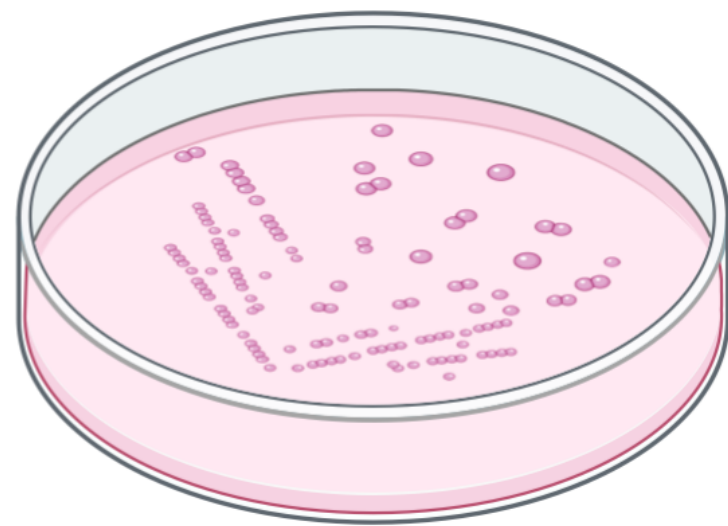
Antifungal Development and Resistance



Challenges in Antifungal Treatment

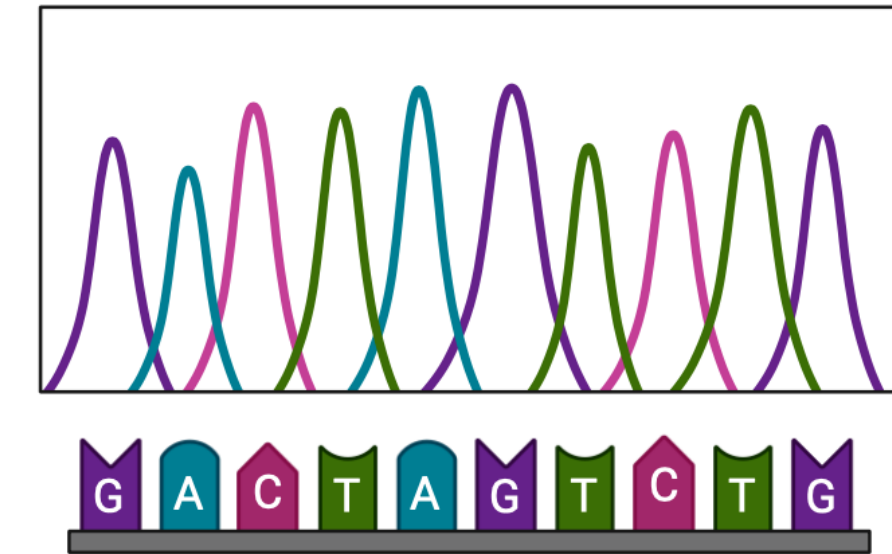
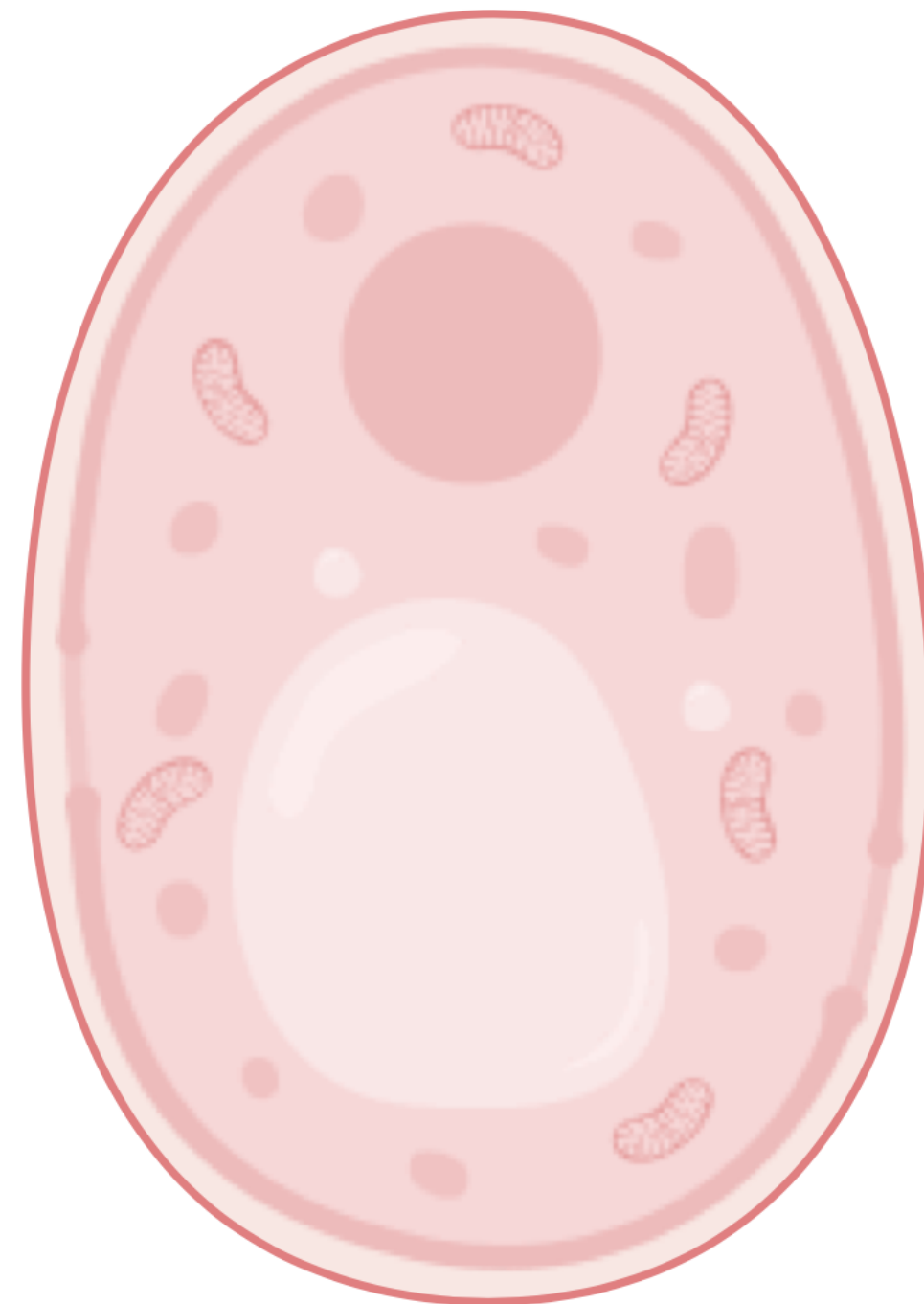


metabolically similar to human cells



significant time to confirmed diagnosis

Fungal Cell

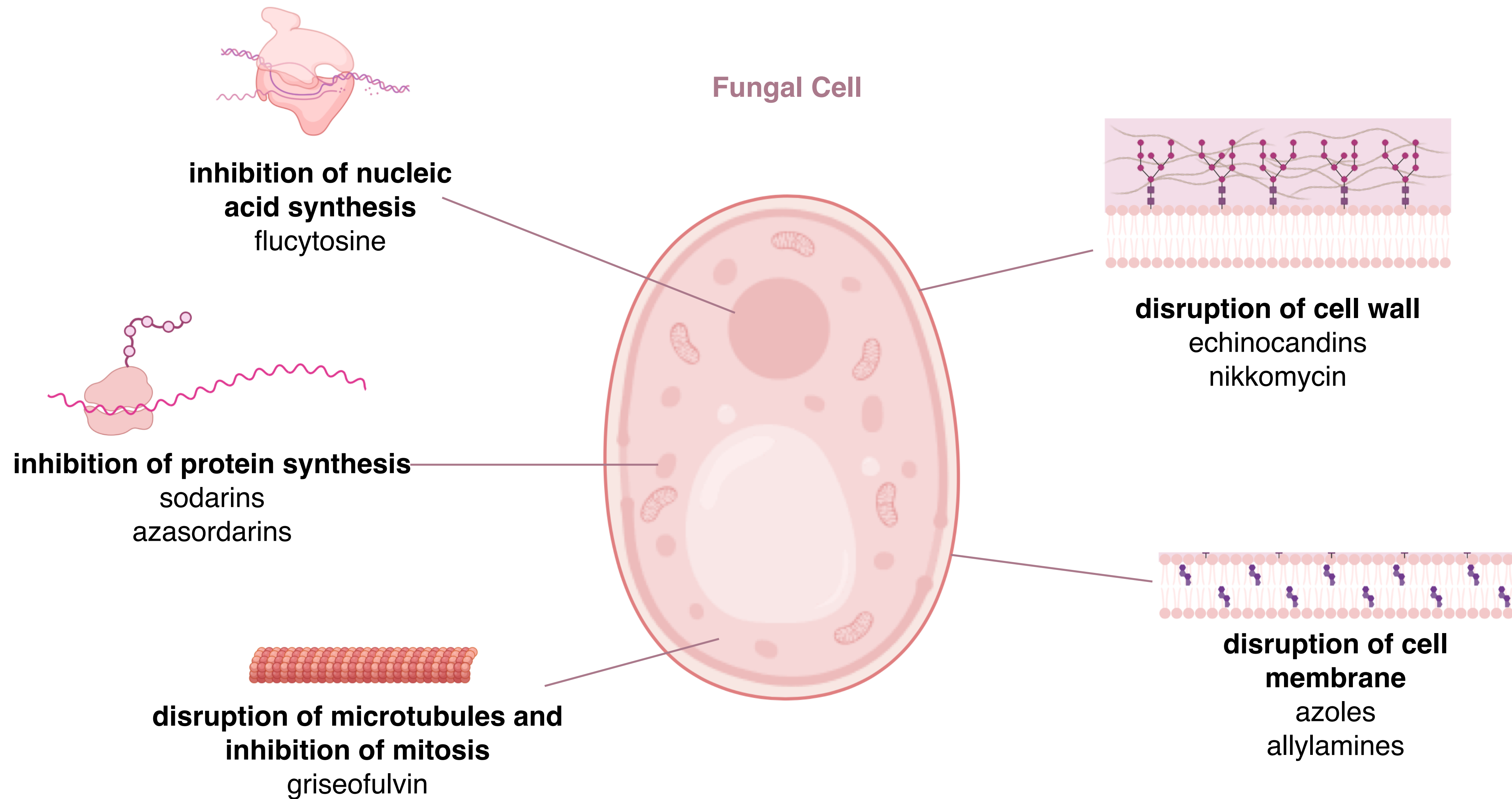


rare strain identification

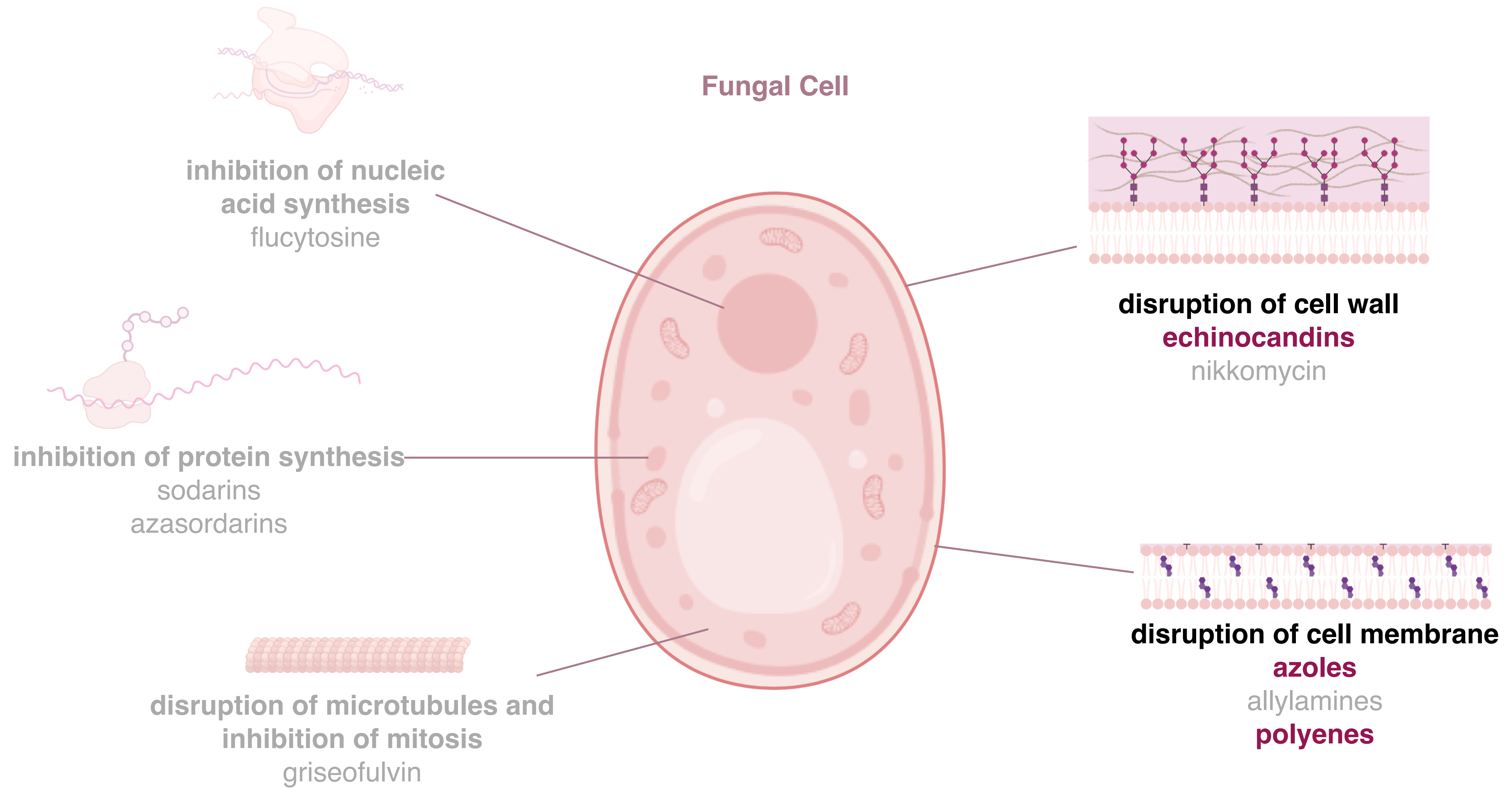


lack of broad spectrum drugs
poor safety profiles

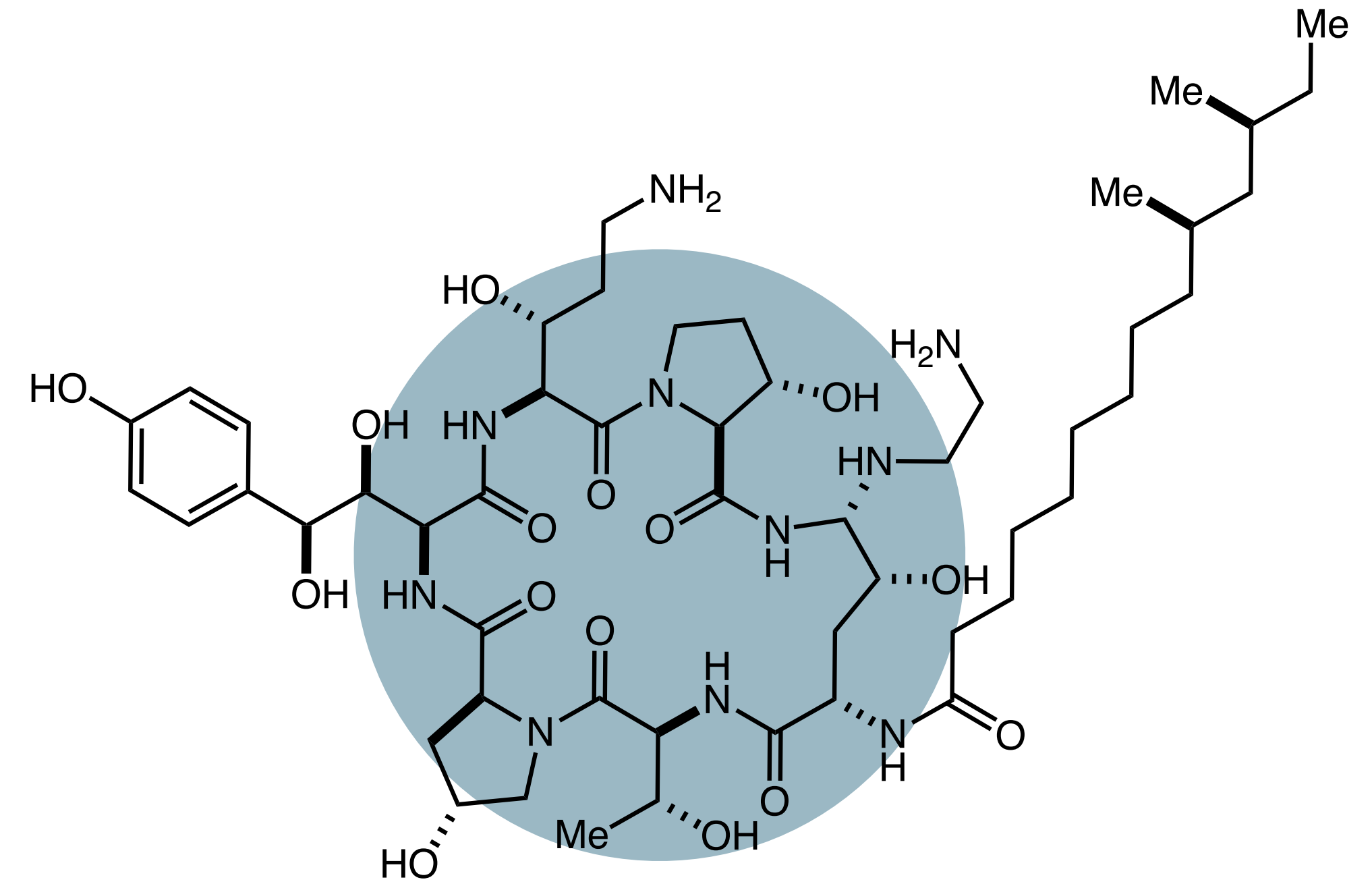
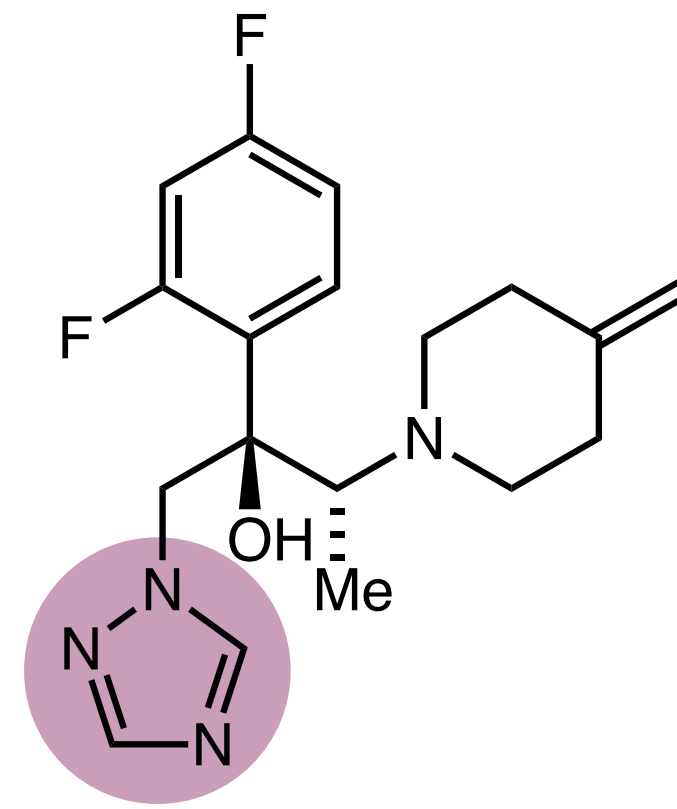
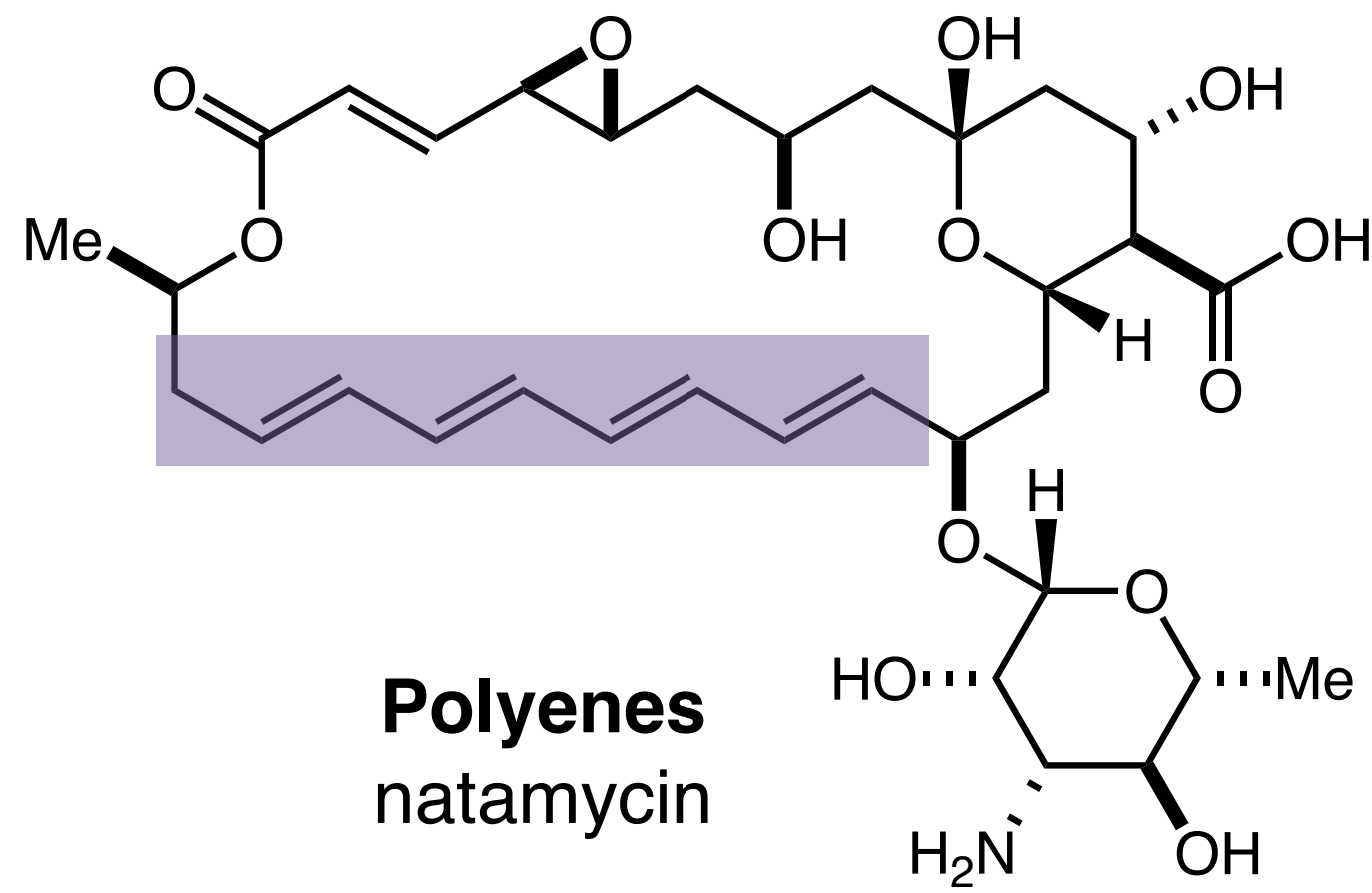
Antifungal Targets



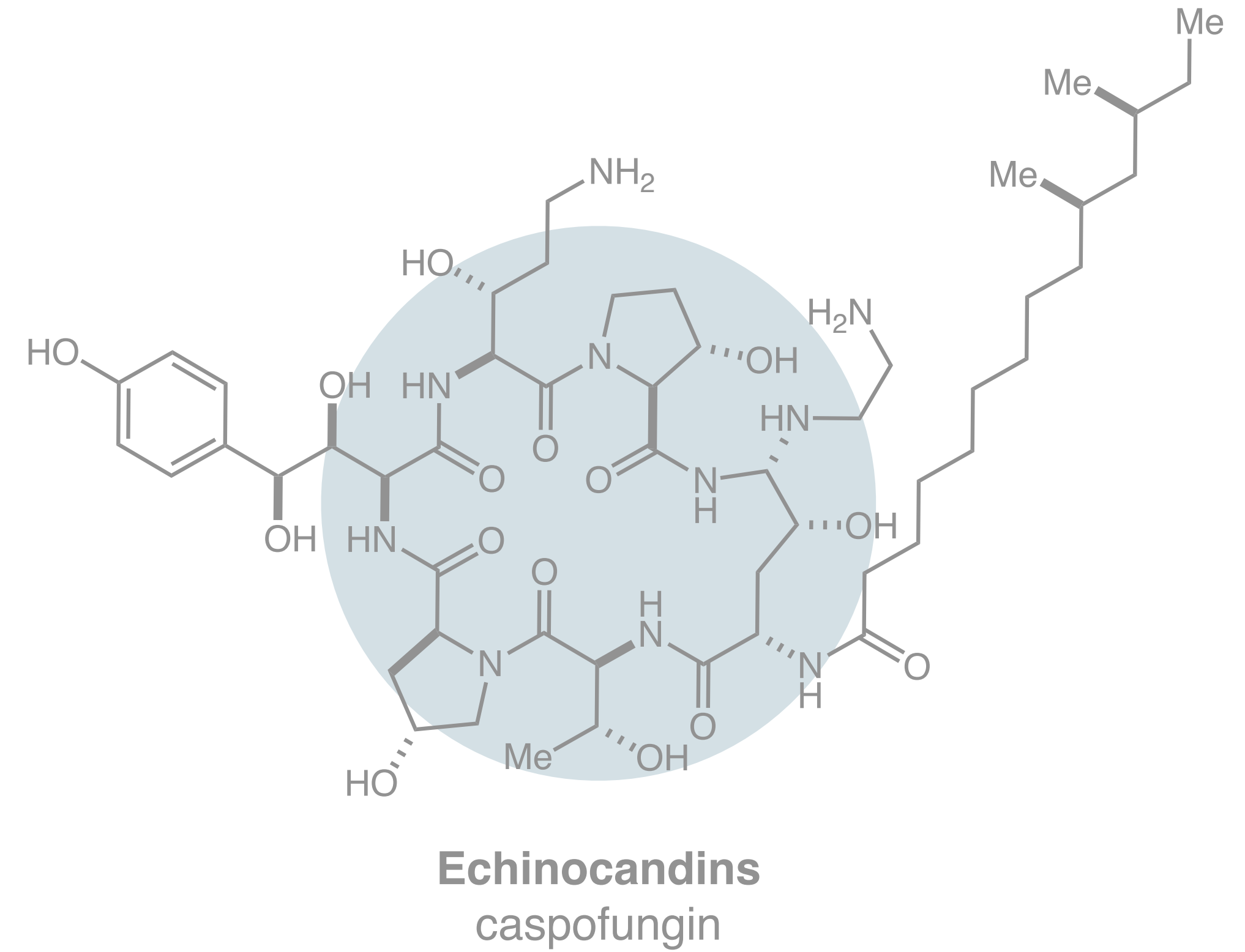
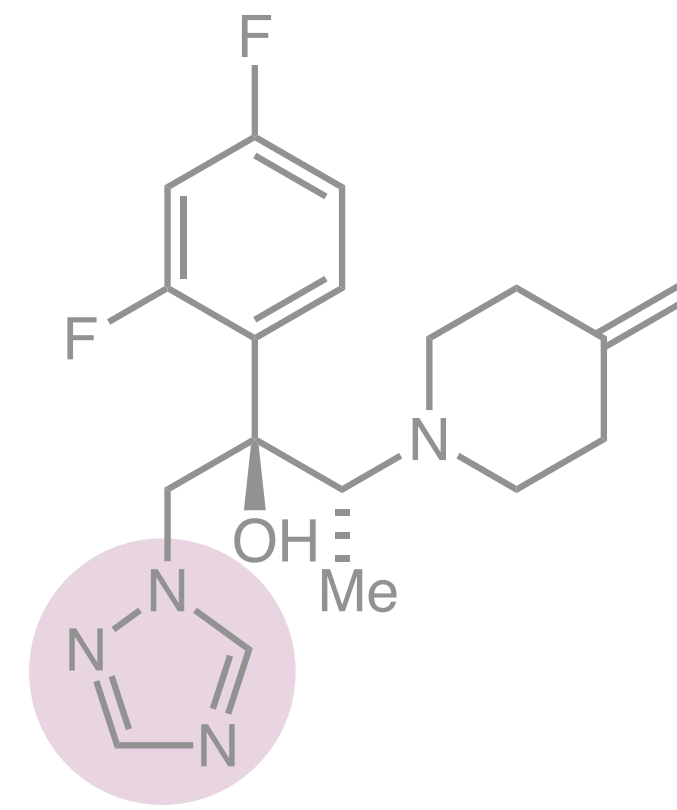
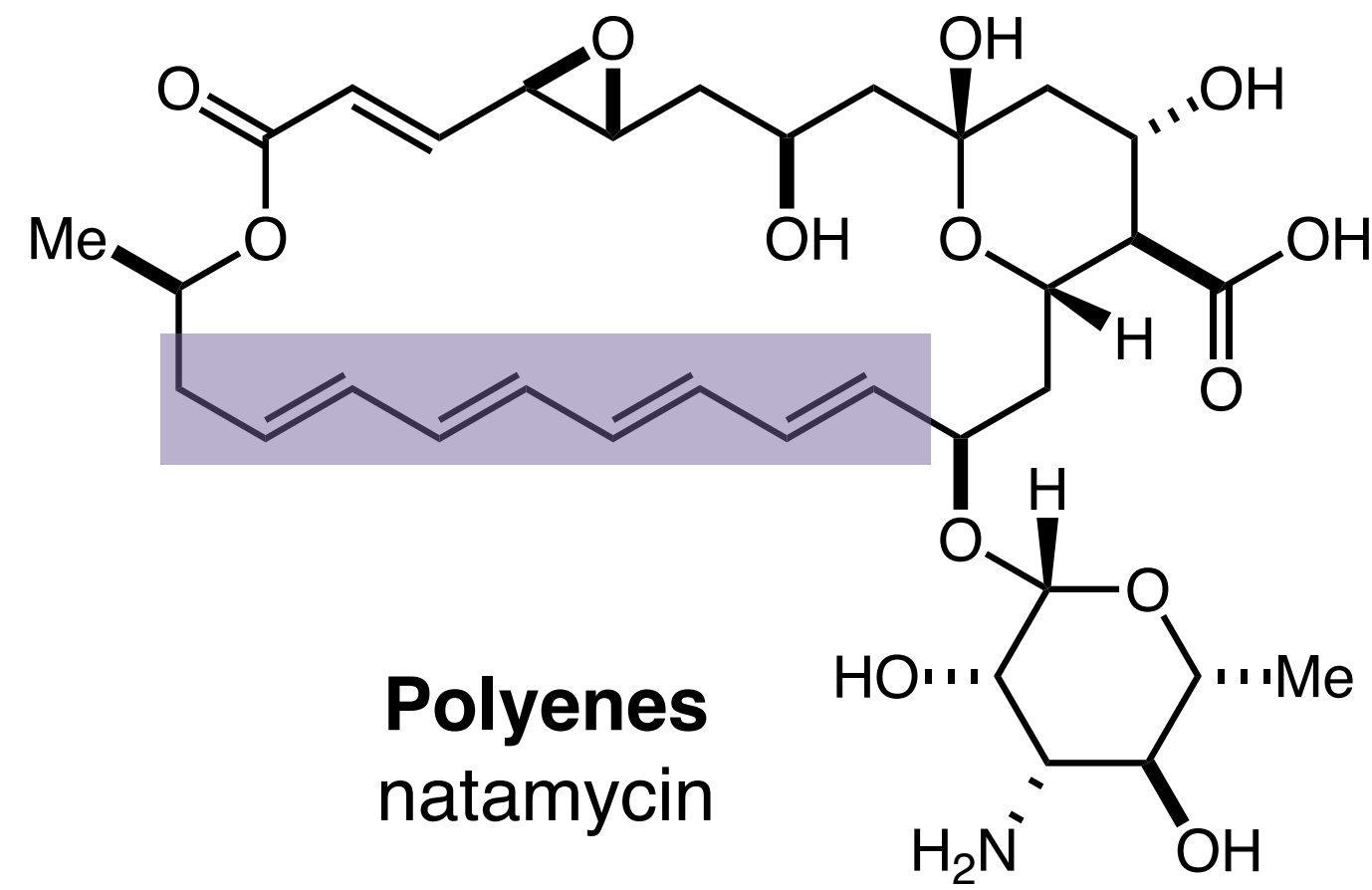
Antifungal Targets



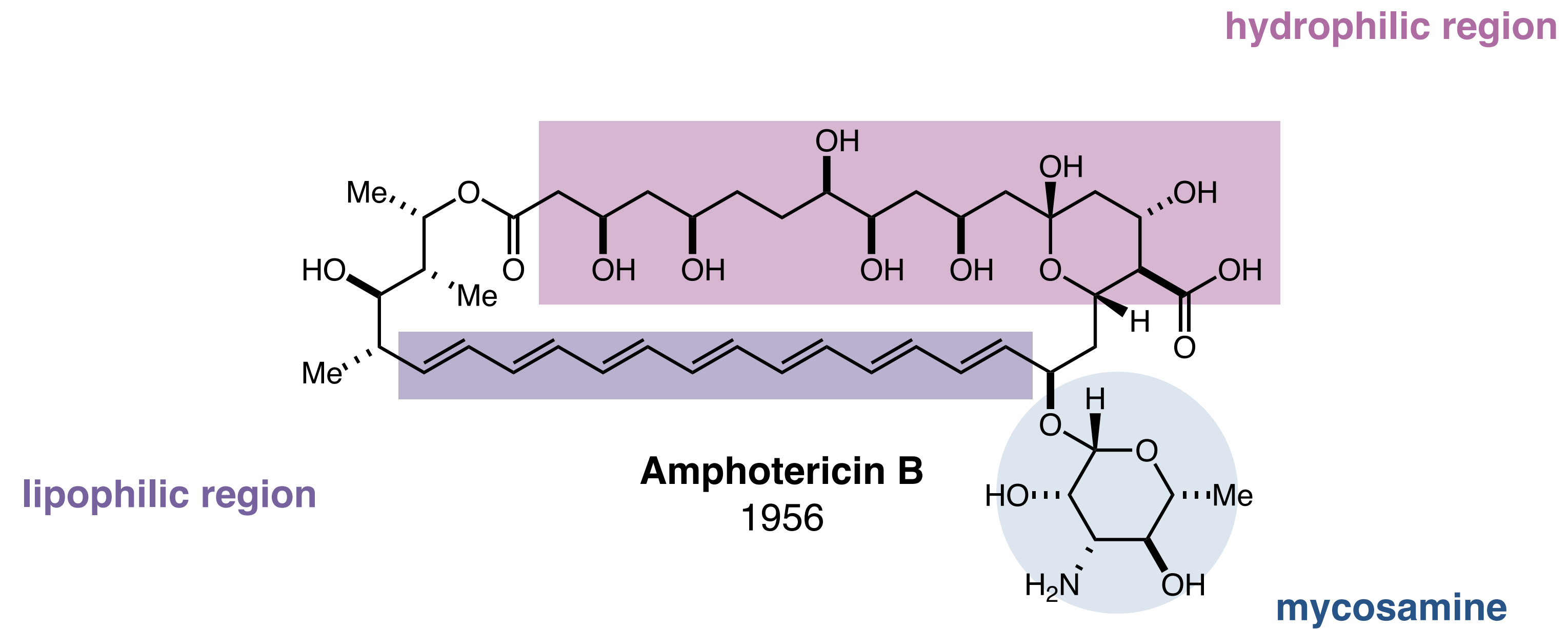
Three Major Classes



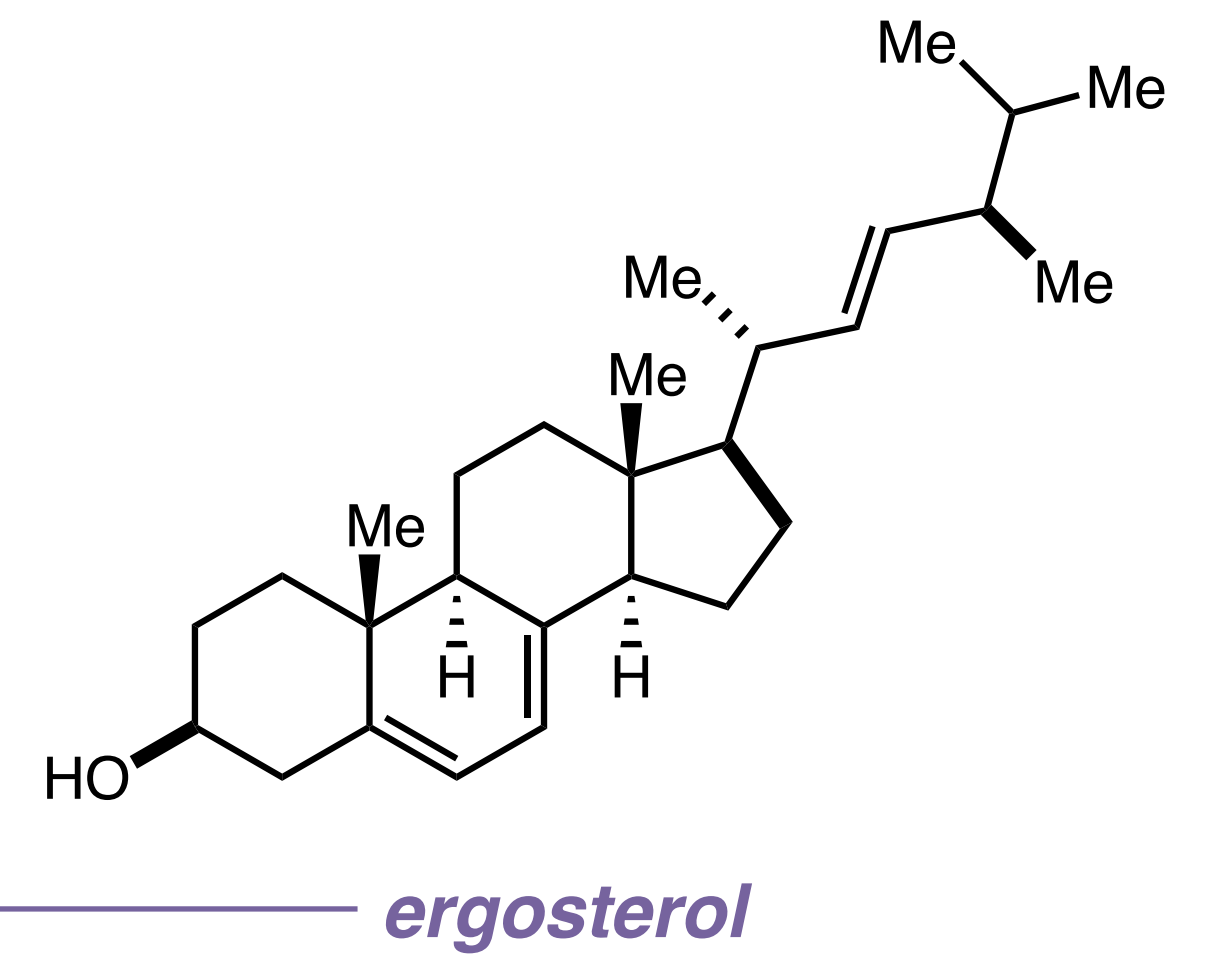
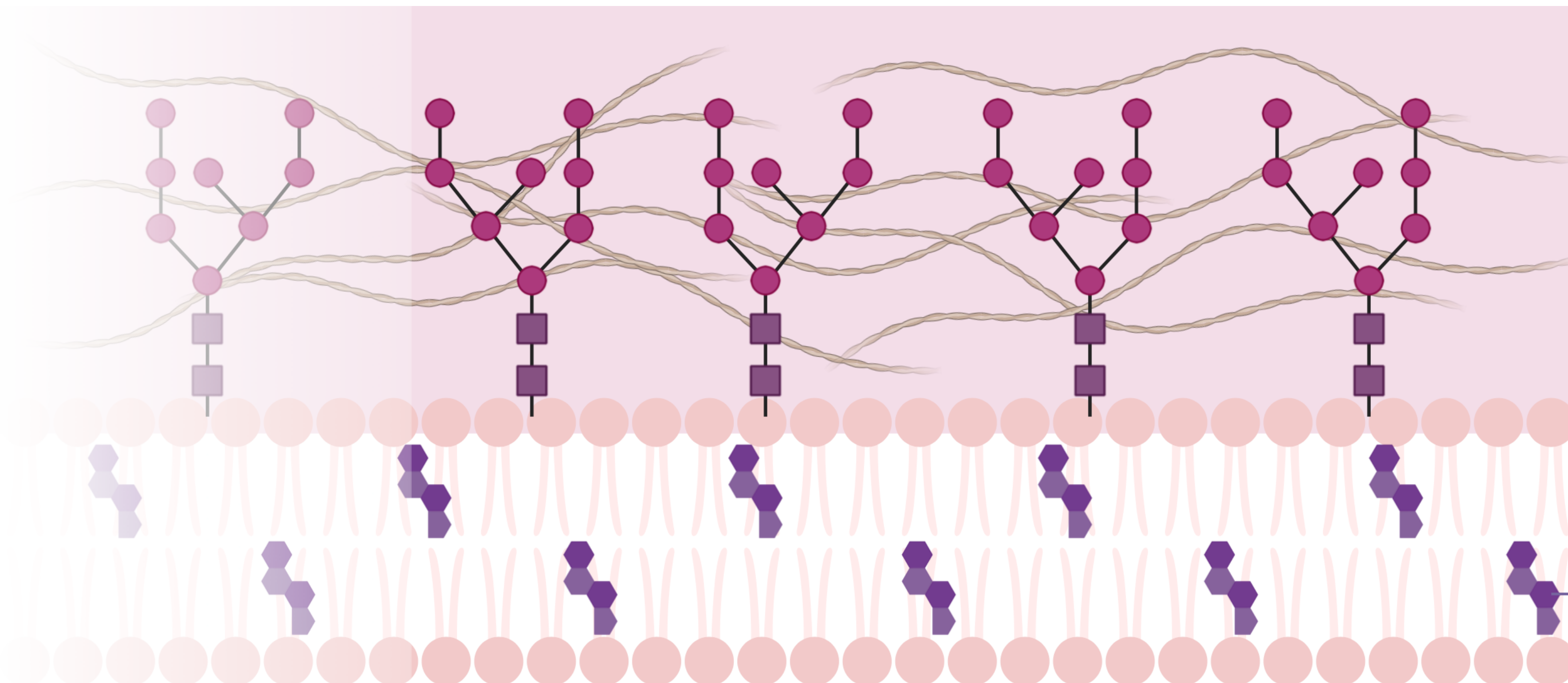
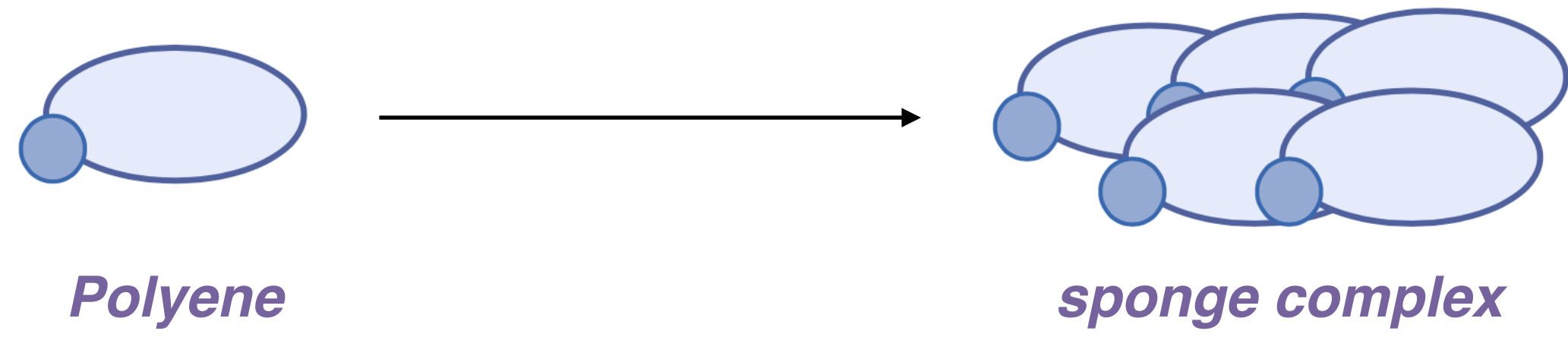
Three Major Classes



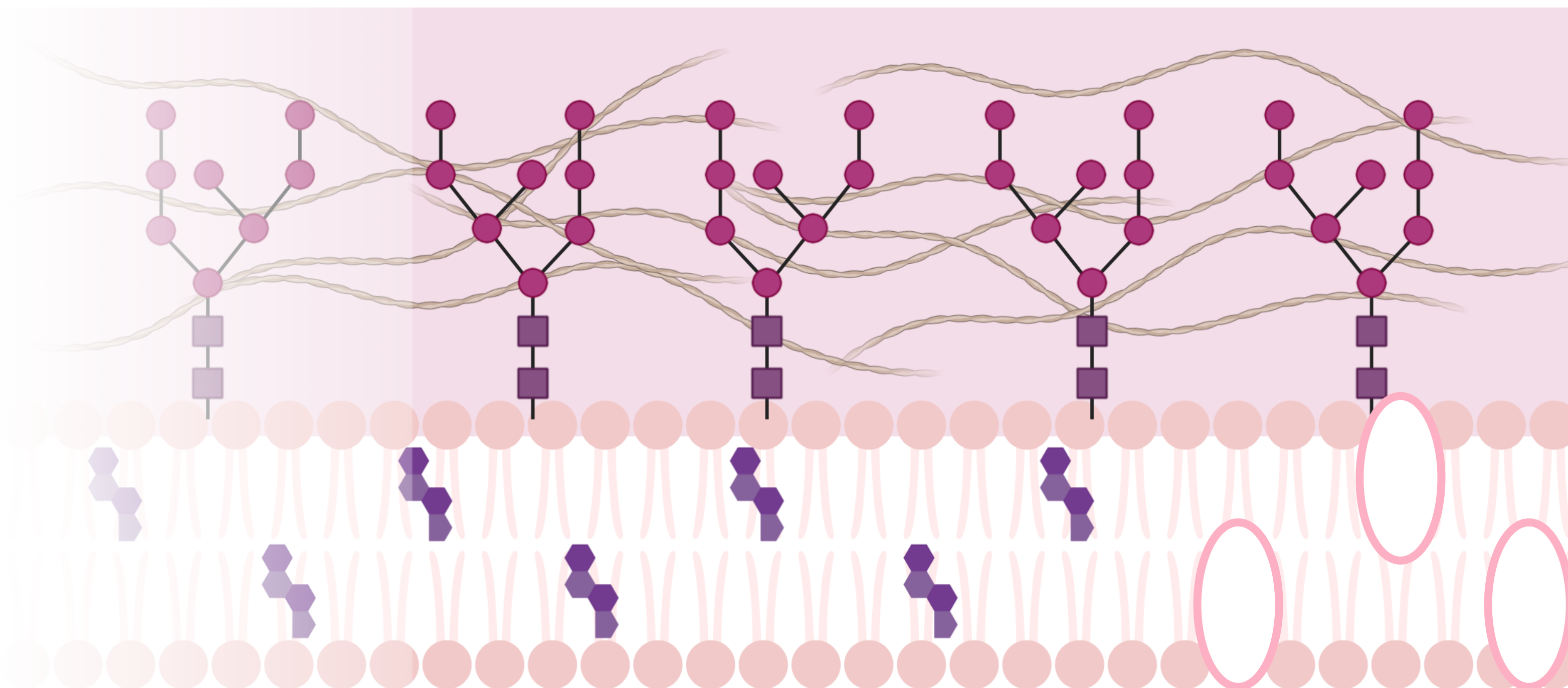
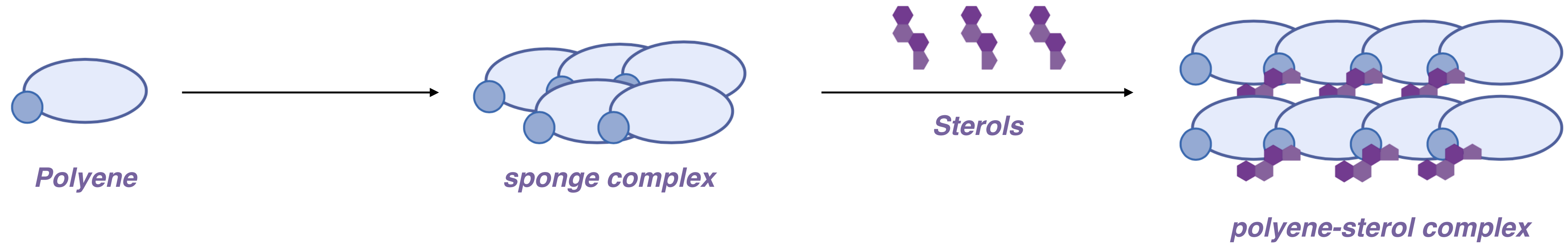
Polyenes



Polyenes – Mechanism of Action



Polyenes – Mechanism of Action

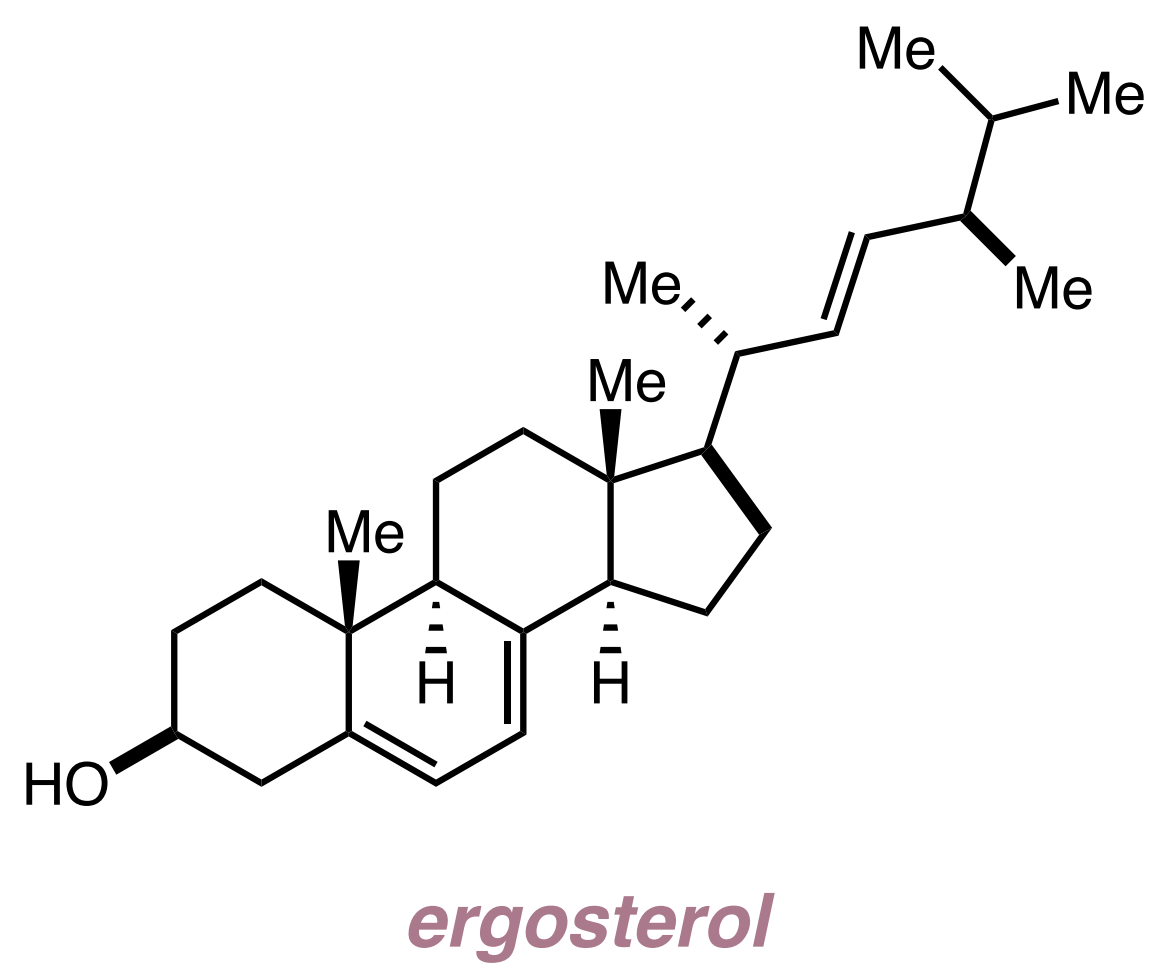


Pore formation
Loss of intracellular ions

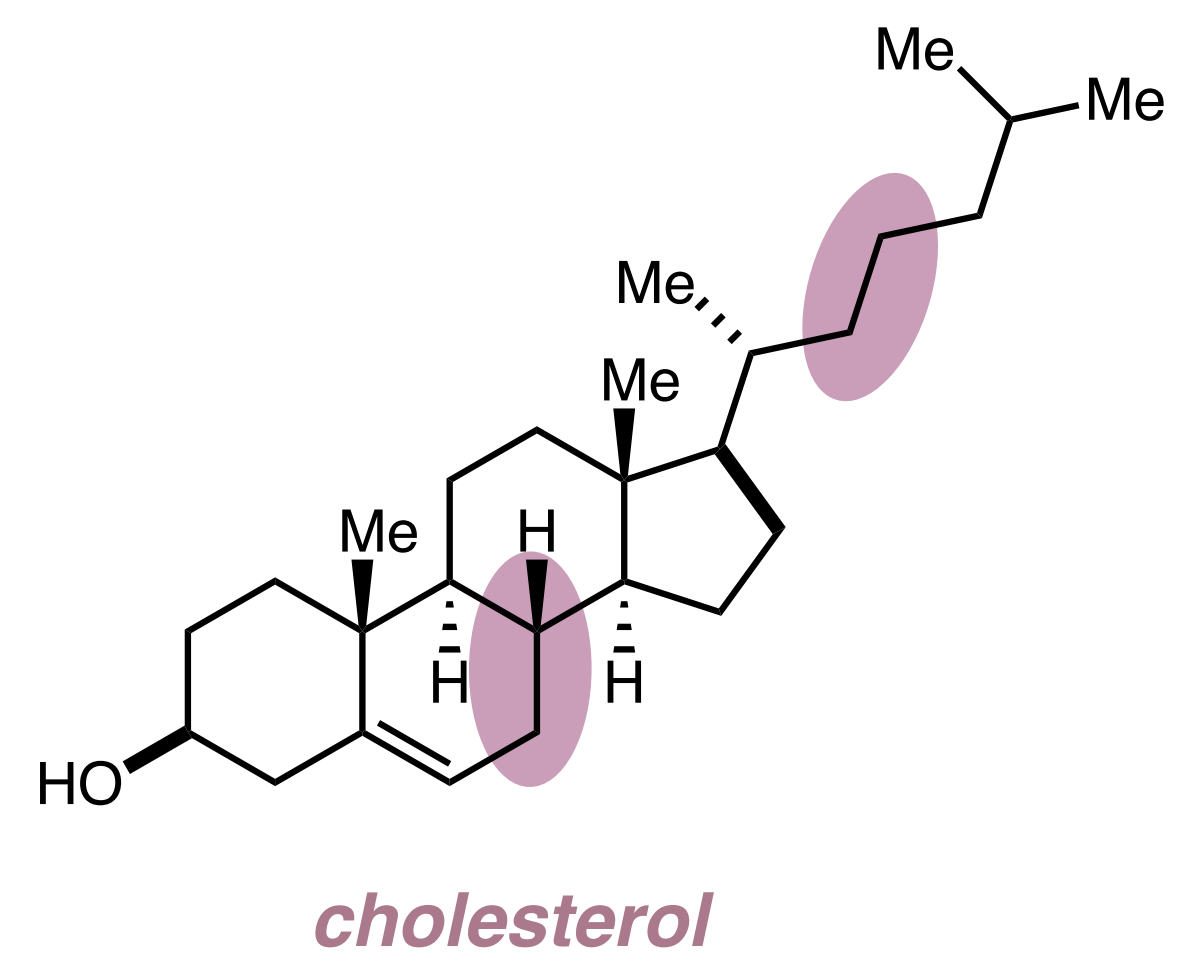
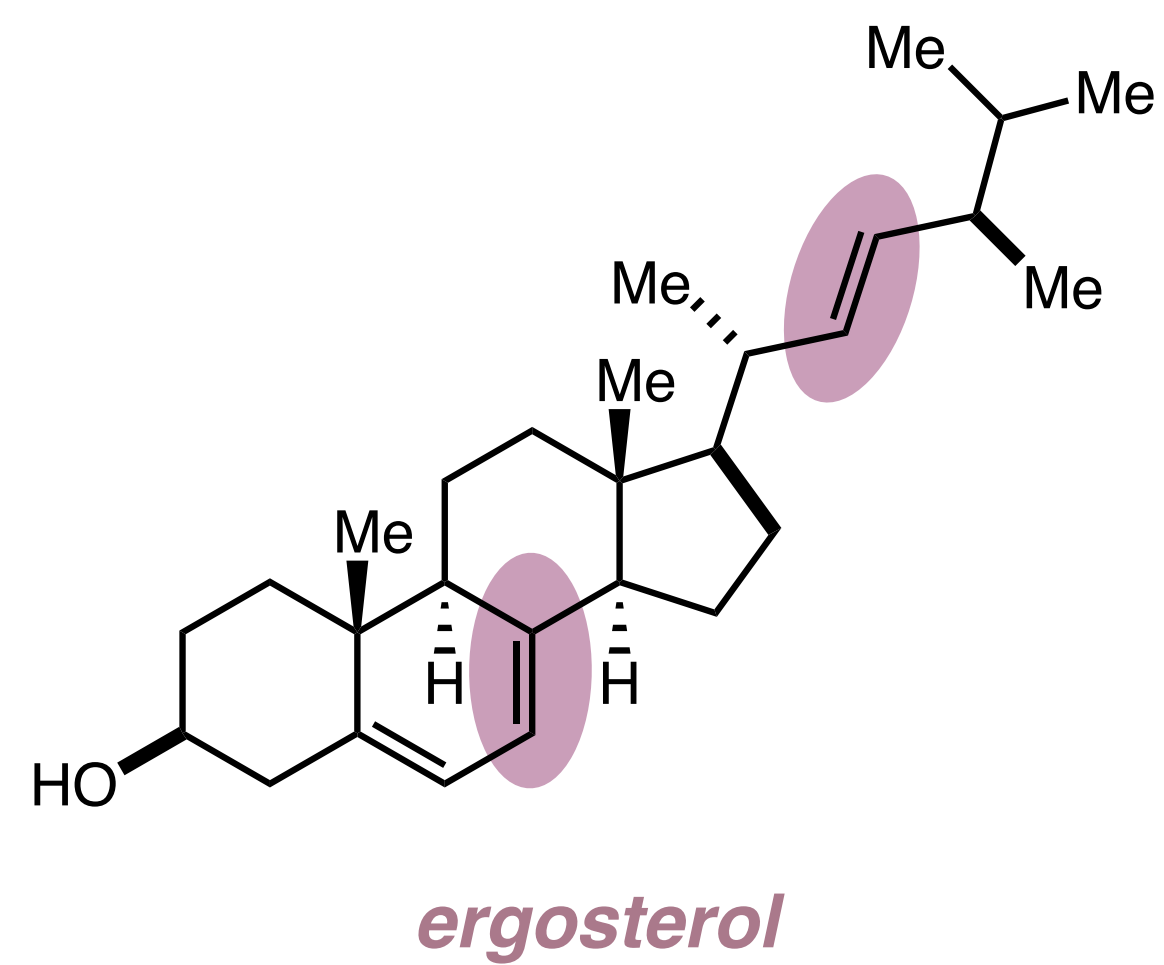
Membrane deformation
Sterol depletion

pores

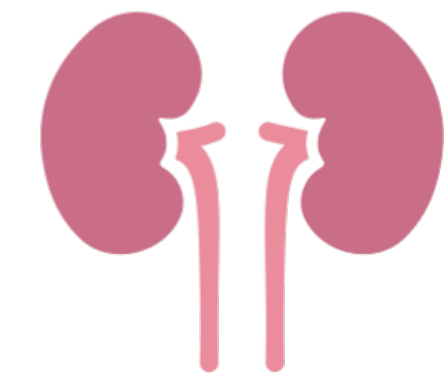
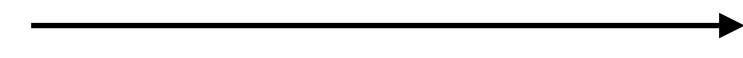
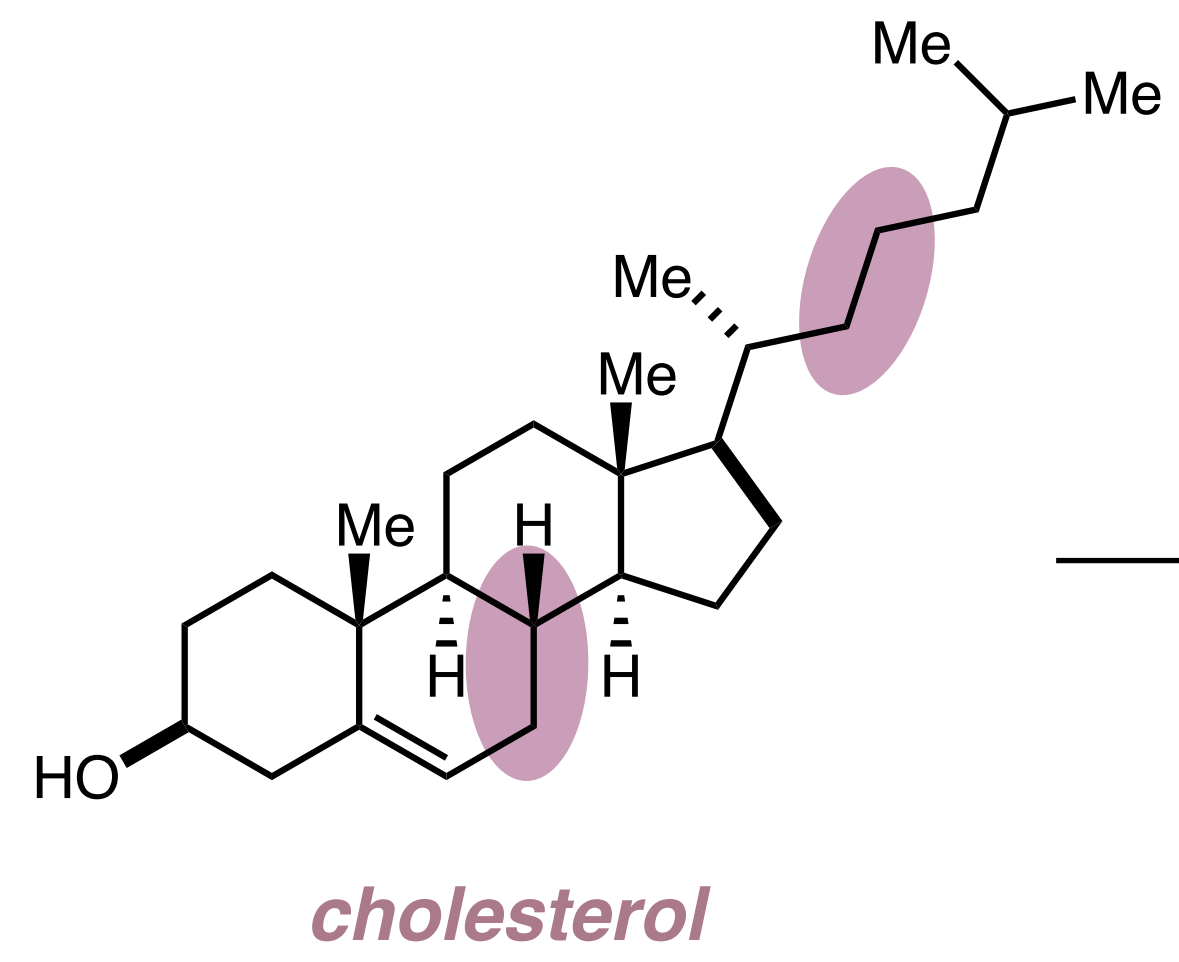
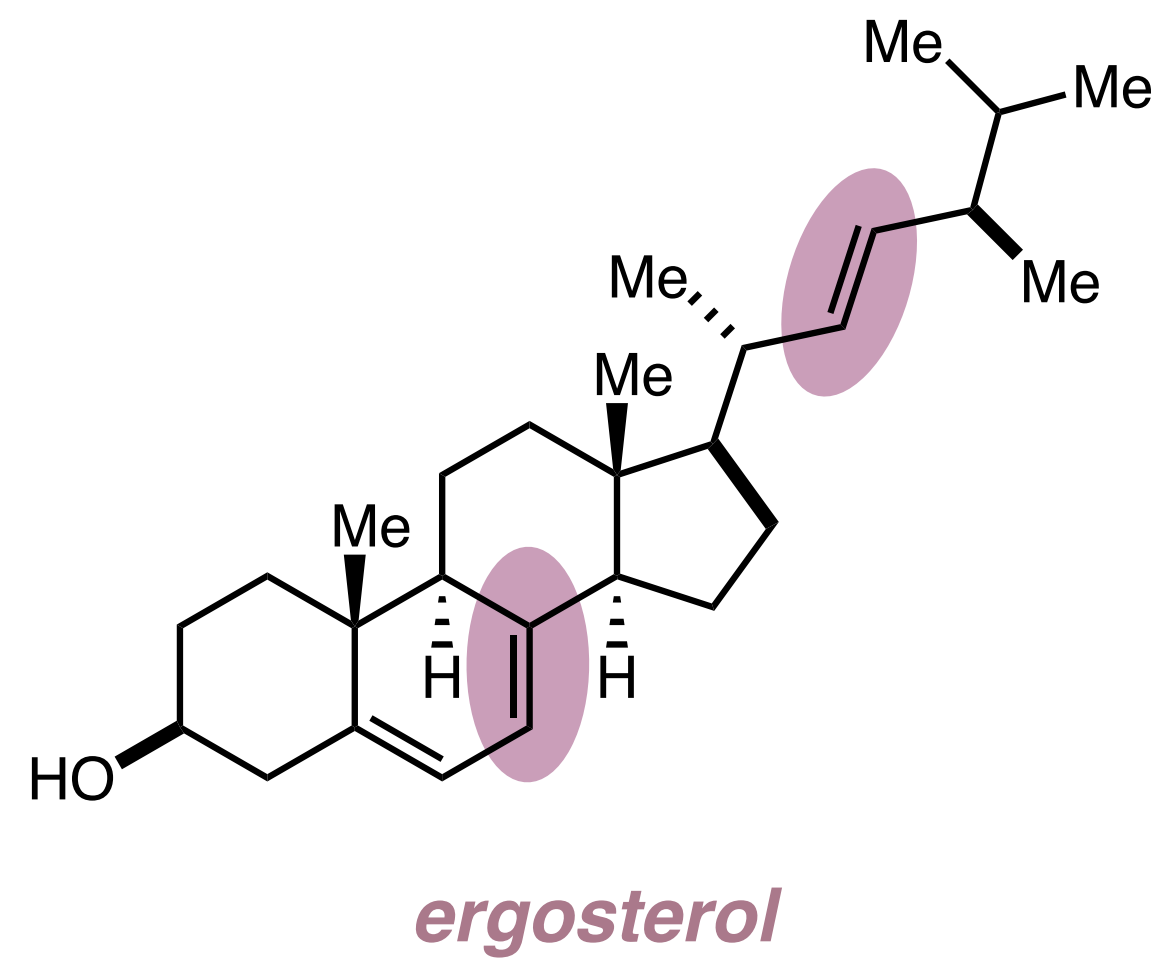
Polyenes – Mechanism of Action



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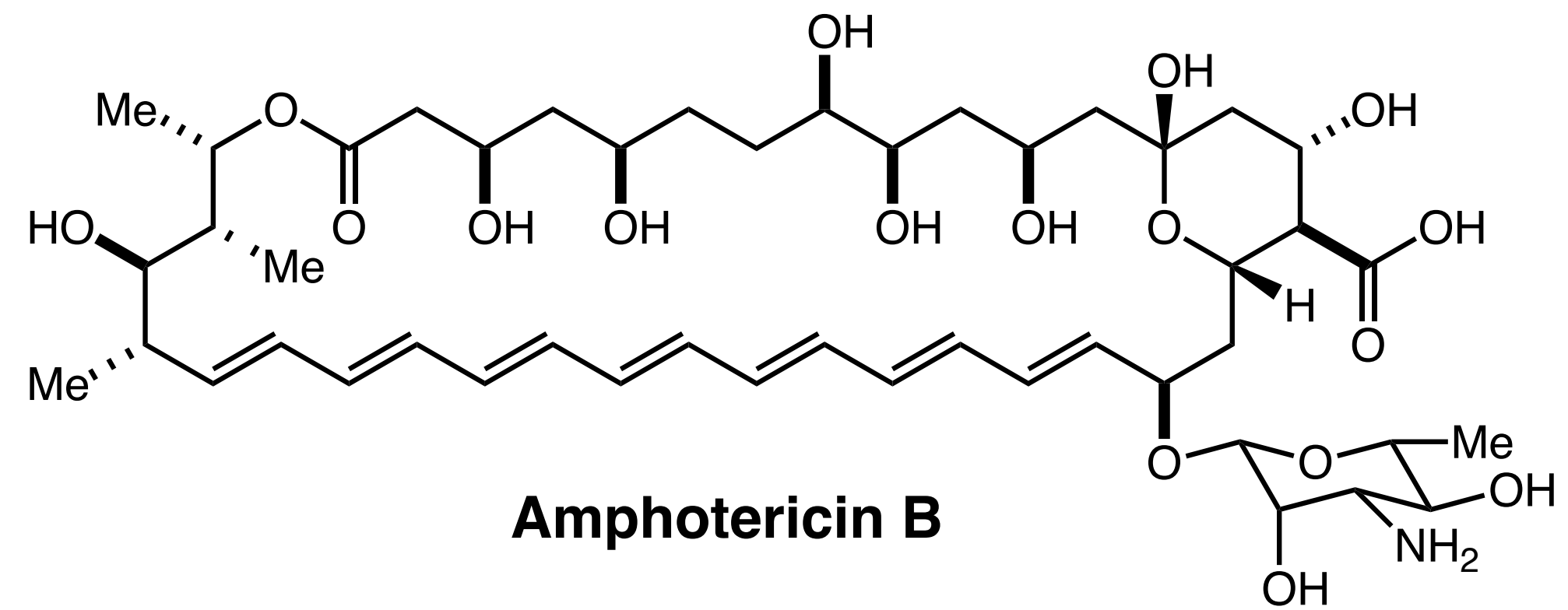


Polyenes – Mechanism of Action

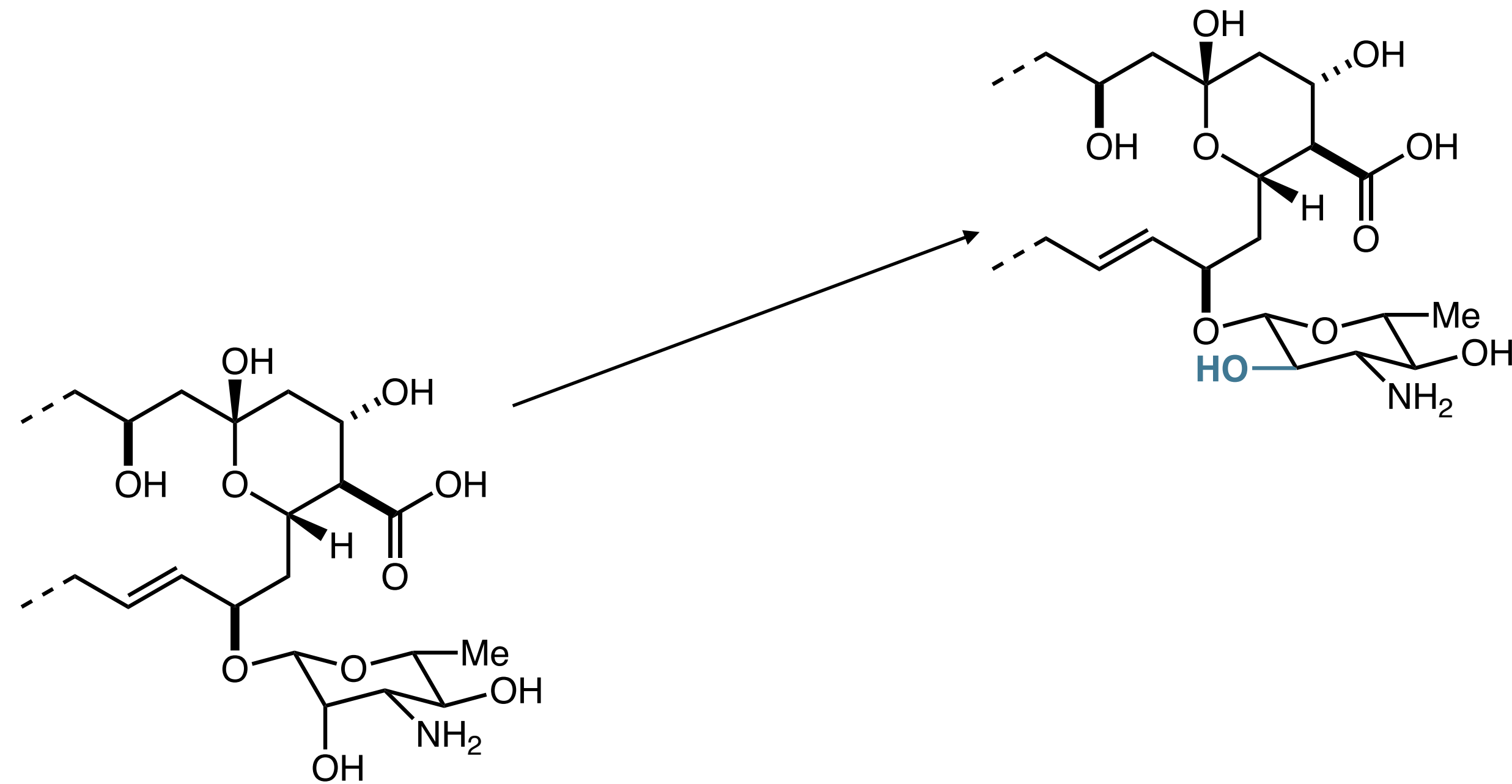


renal toxicity

Elion Therapeutics – Amphotericin B Derivative



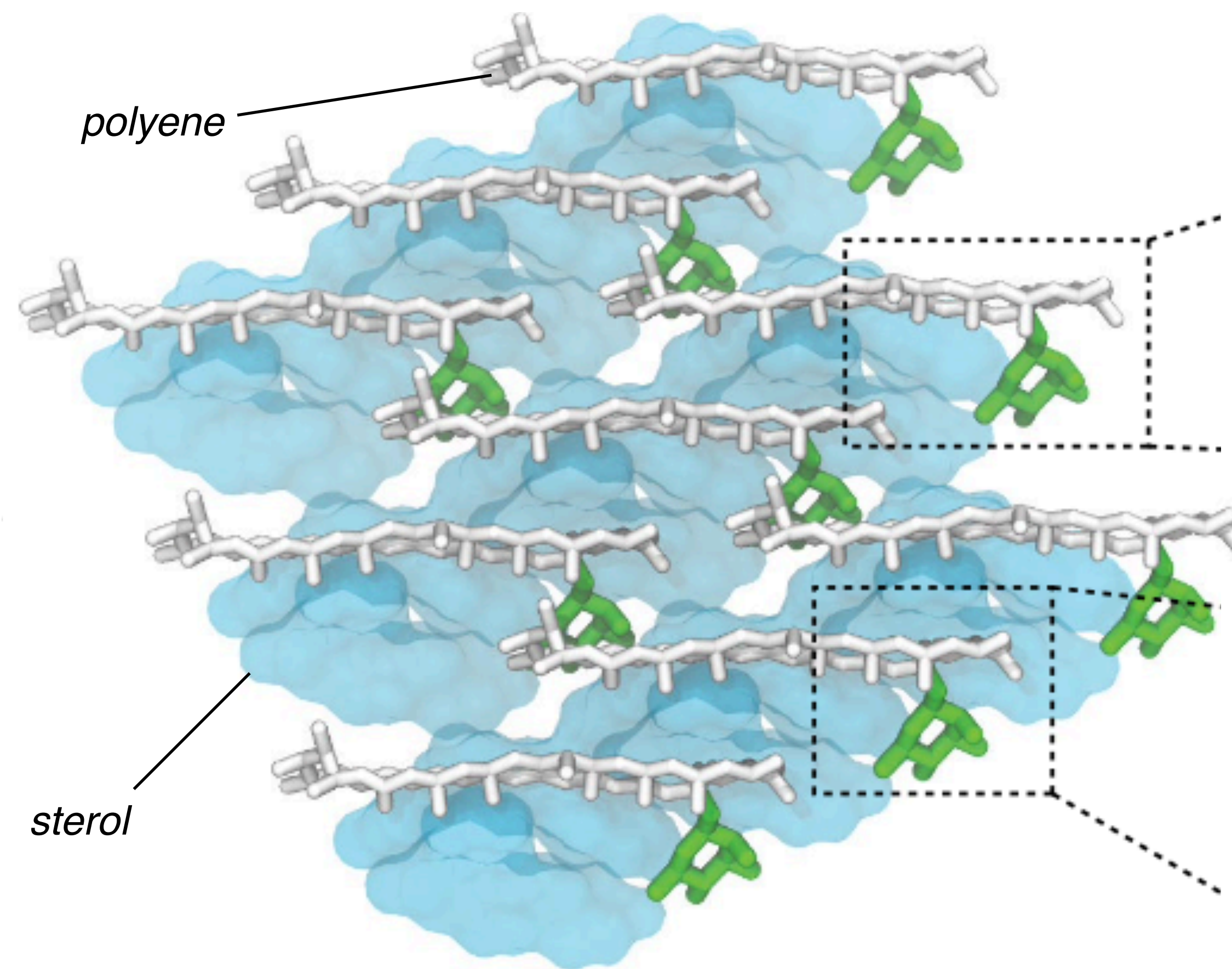
Elion Therapeutics – Amphotericin B Derivative



C2'EpiAmpB

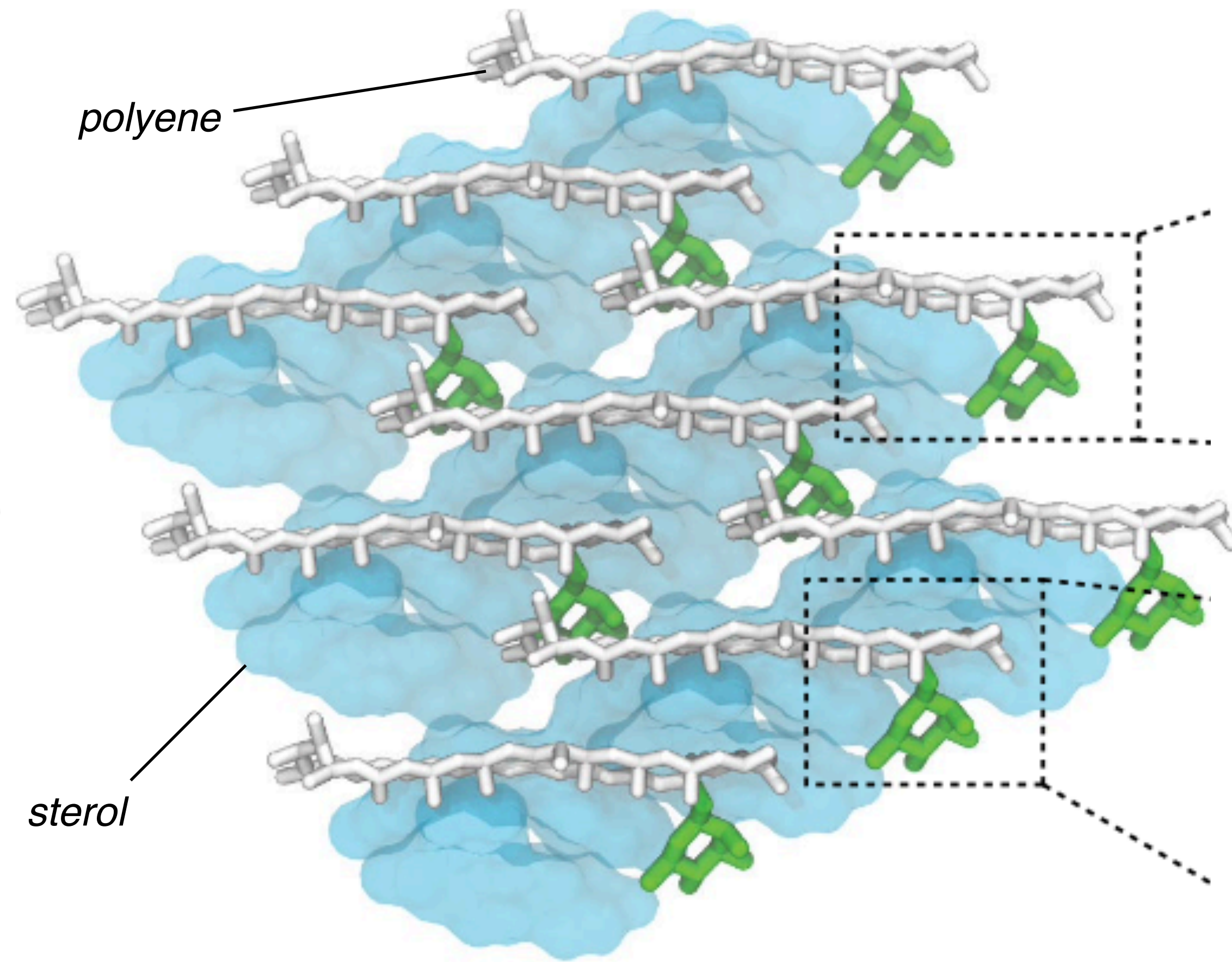
Amphotericin B
potent
renal toxic

Elion Therapeutics – Amphotericin B Derivative



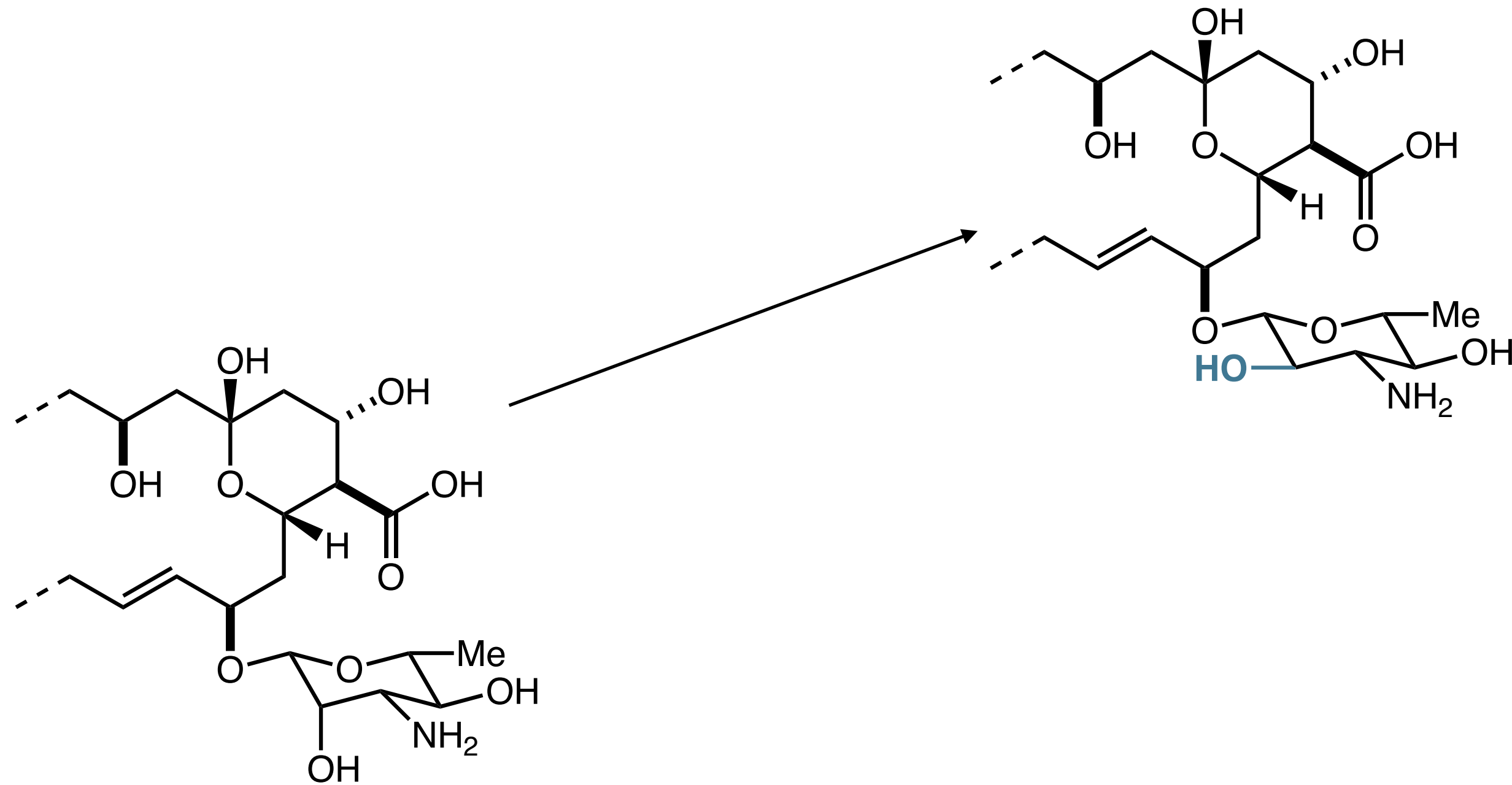
Sterol Sponge Complex

Elion Therapeutics – Amphotericin B Derivative



Sterol Sponge Complex

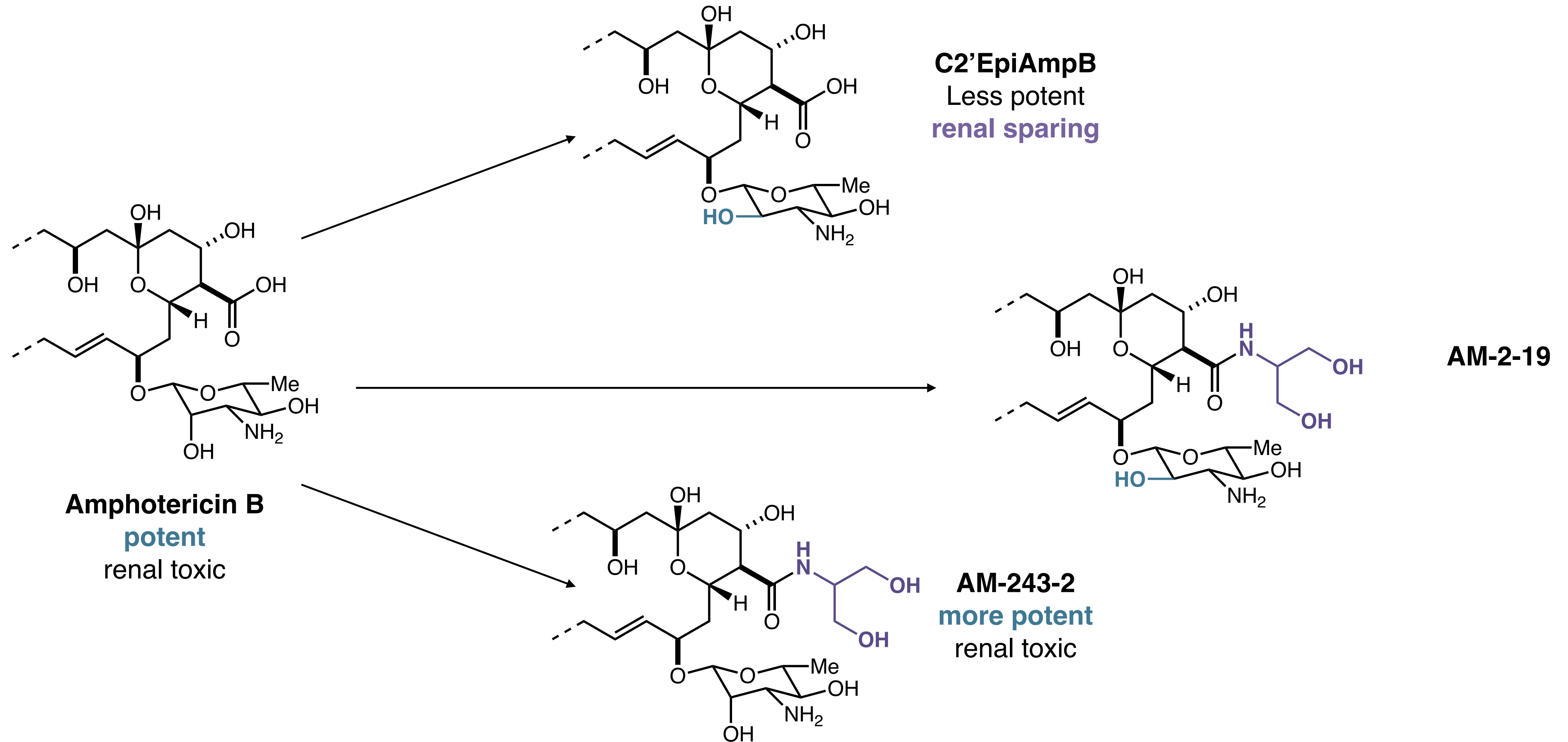
Elion Therapeutics – Amphotericin B Derivative



Amphotericin B
potent
renal toxic

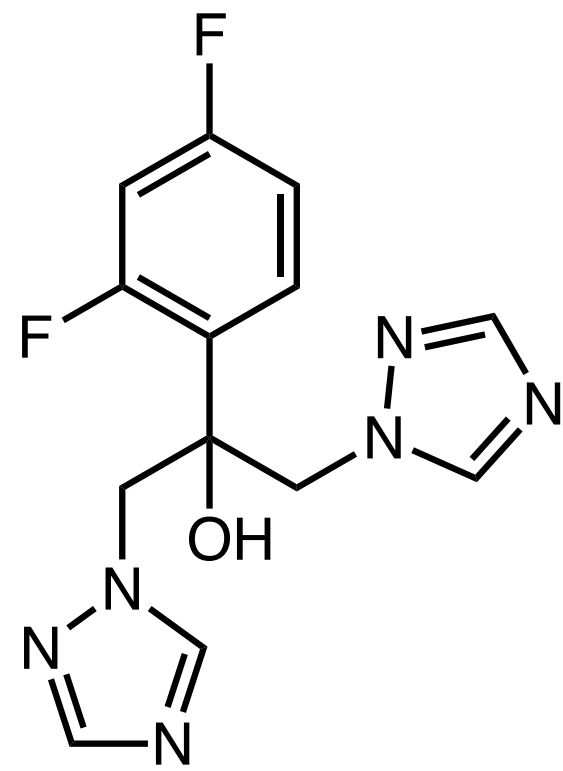
C2'EpiAmpB
Less potent
renal sparing

Elion Therapeutics – Amphotericin B Derivative

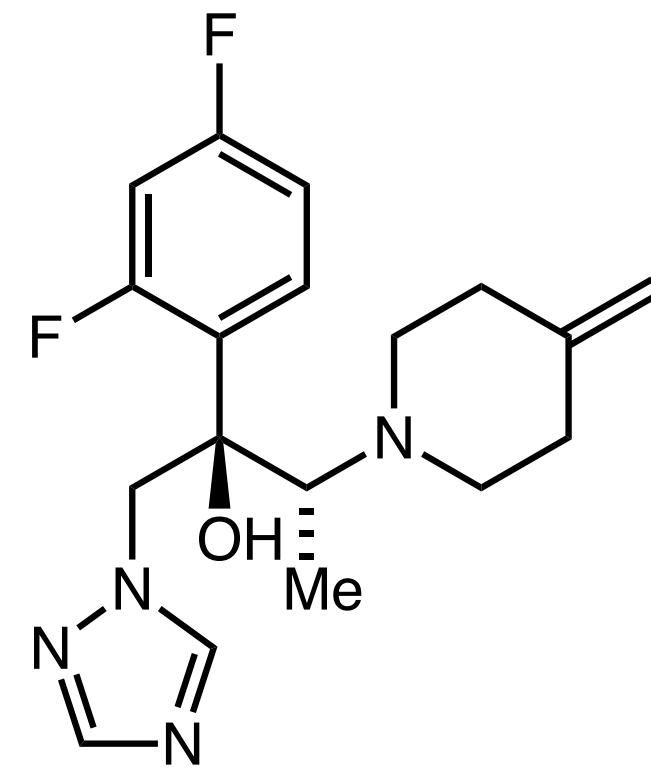


Azoles

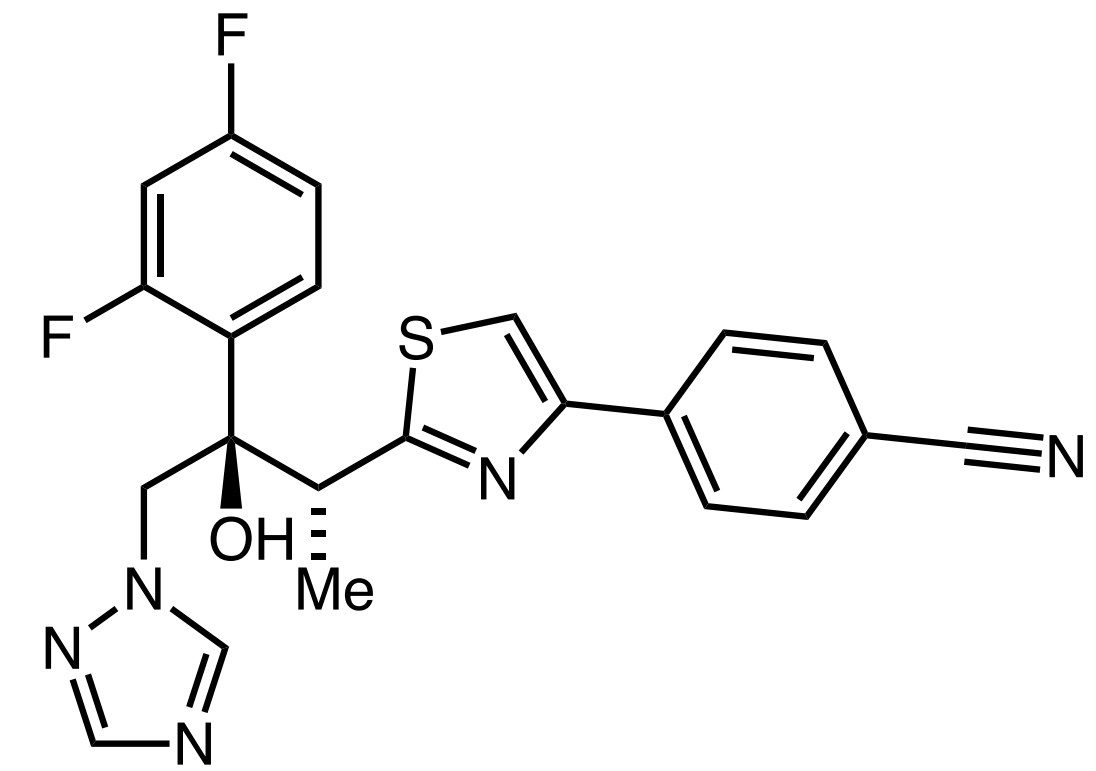
Azoles



Fluconazole
1990

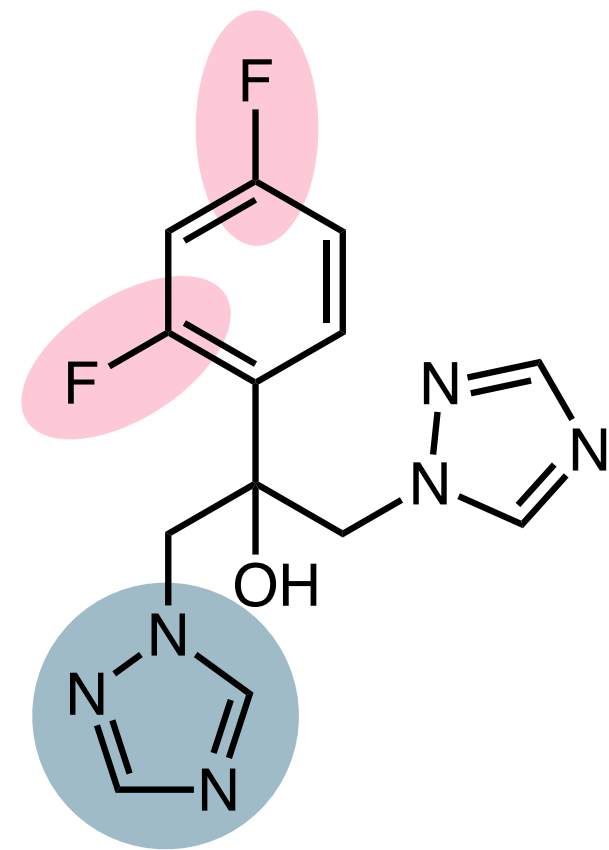


EFINAZOLE
2014

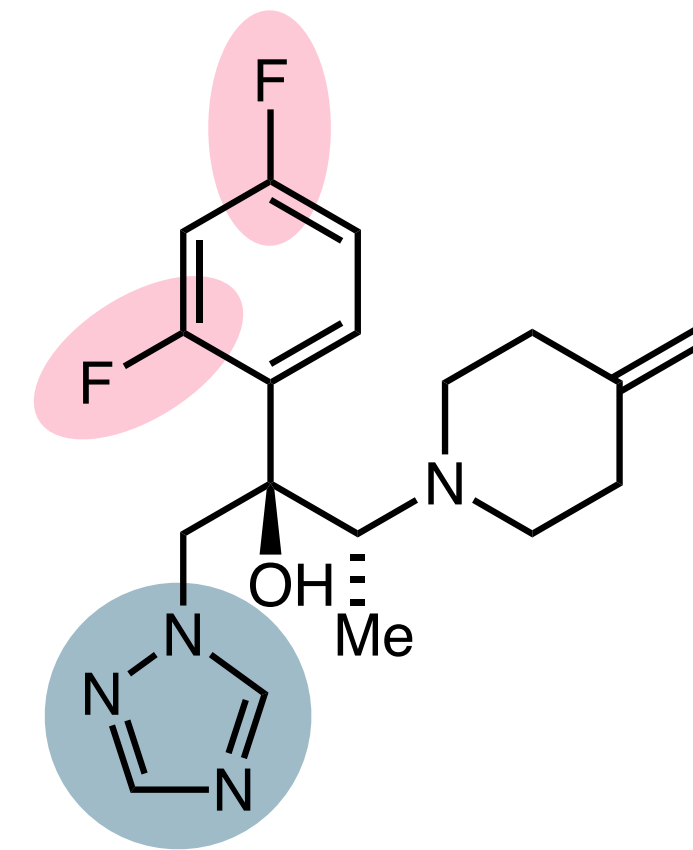


Isavuconazole
2015

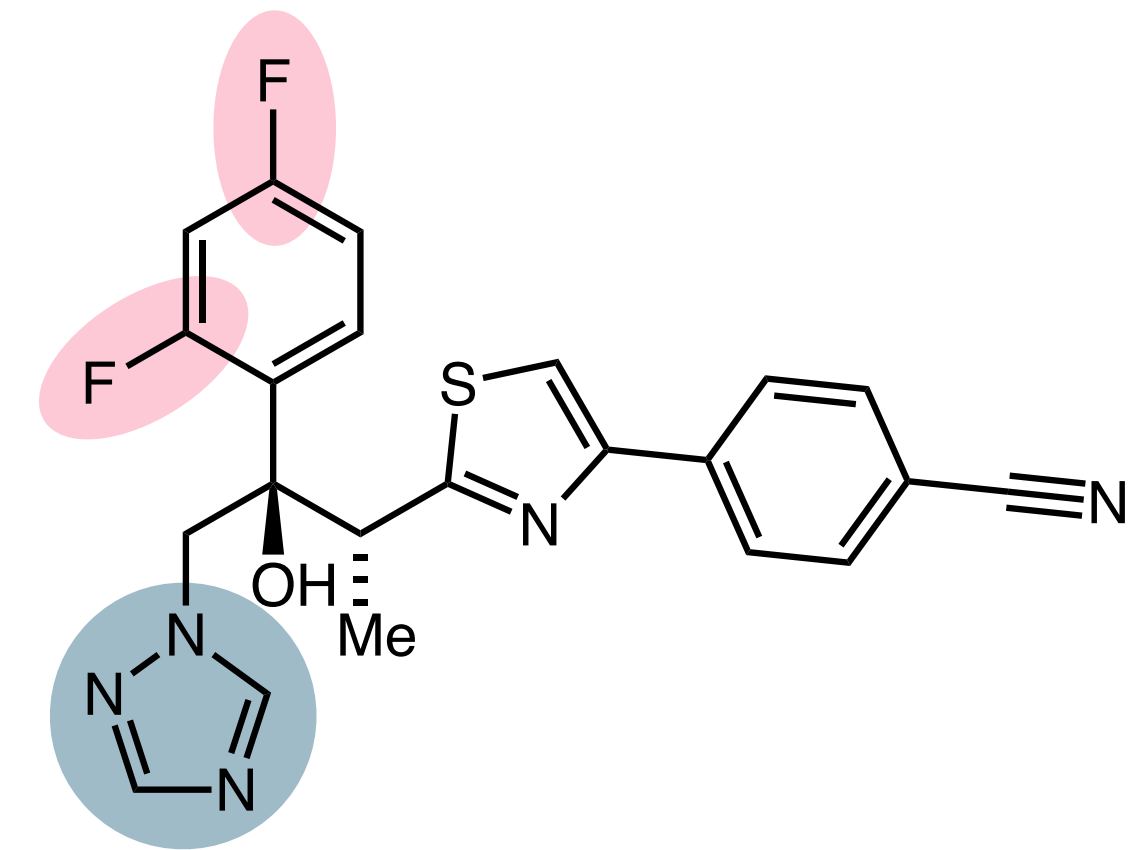
Azoles



Fluconazole
1990

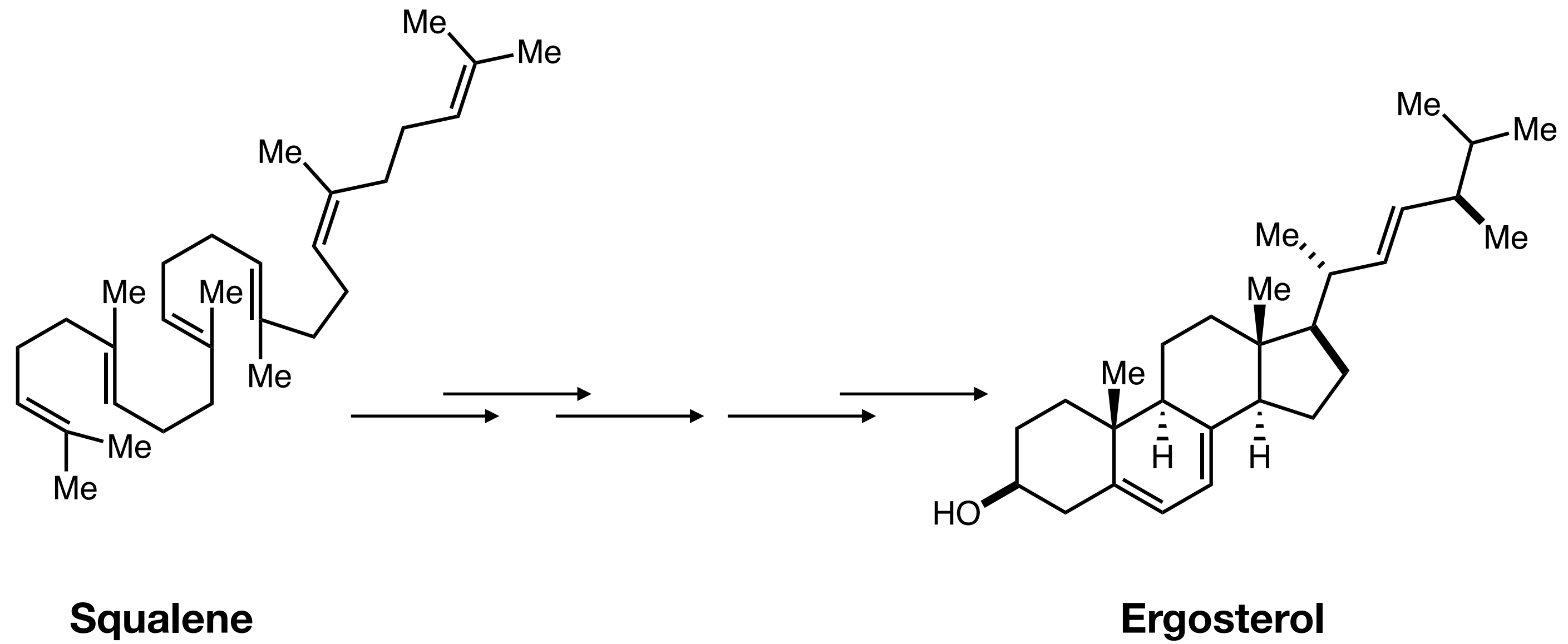


Efinaconazole
2014

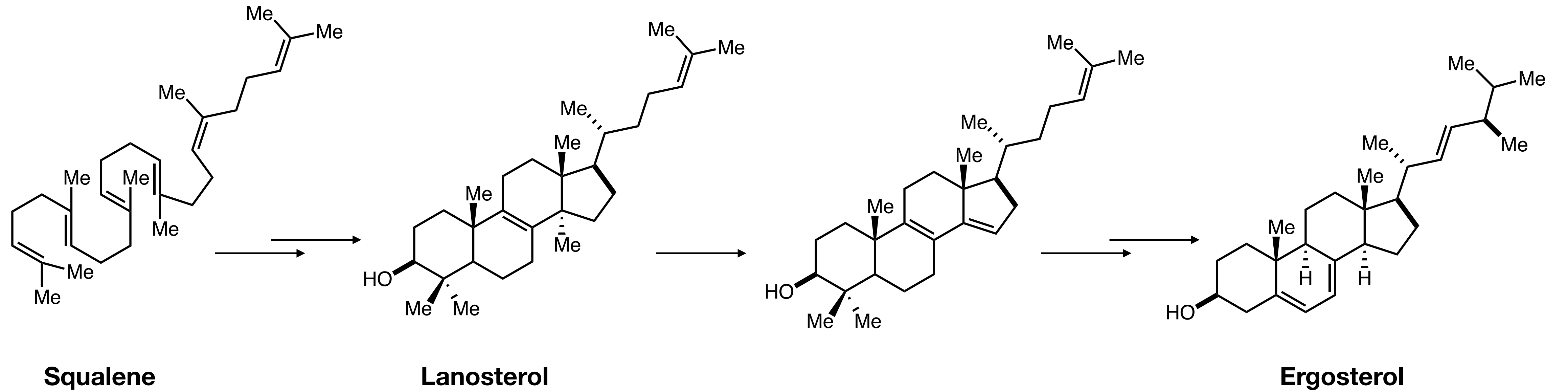


Isavuconazole
2015

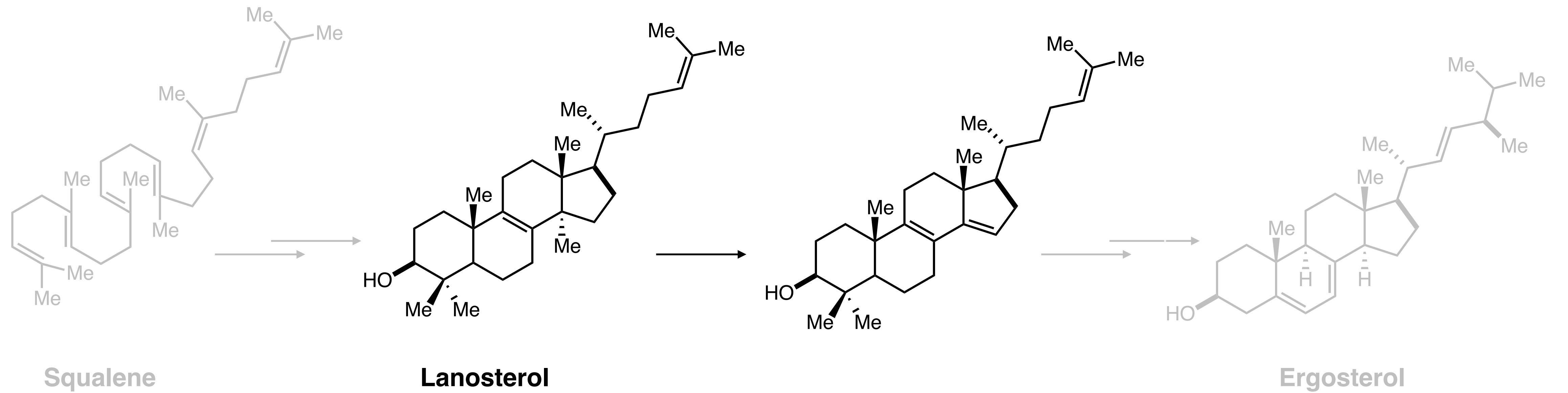
Azole Target – Ergosterol Biosynthesis



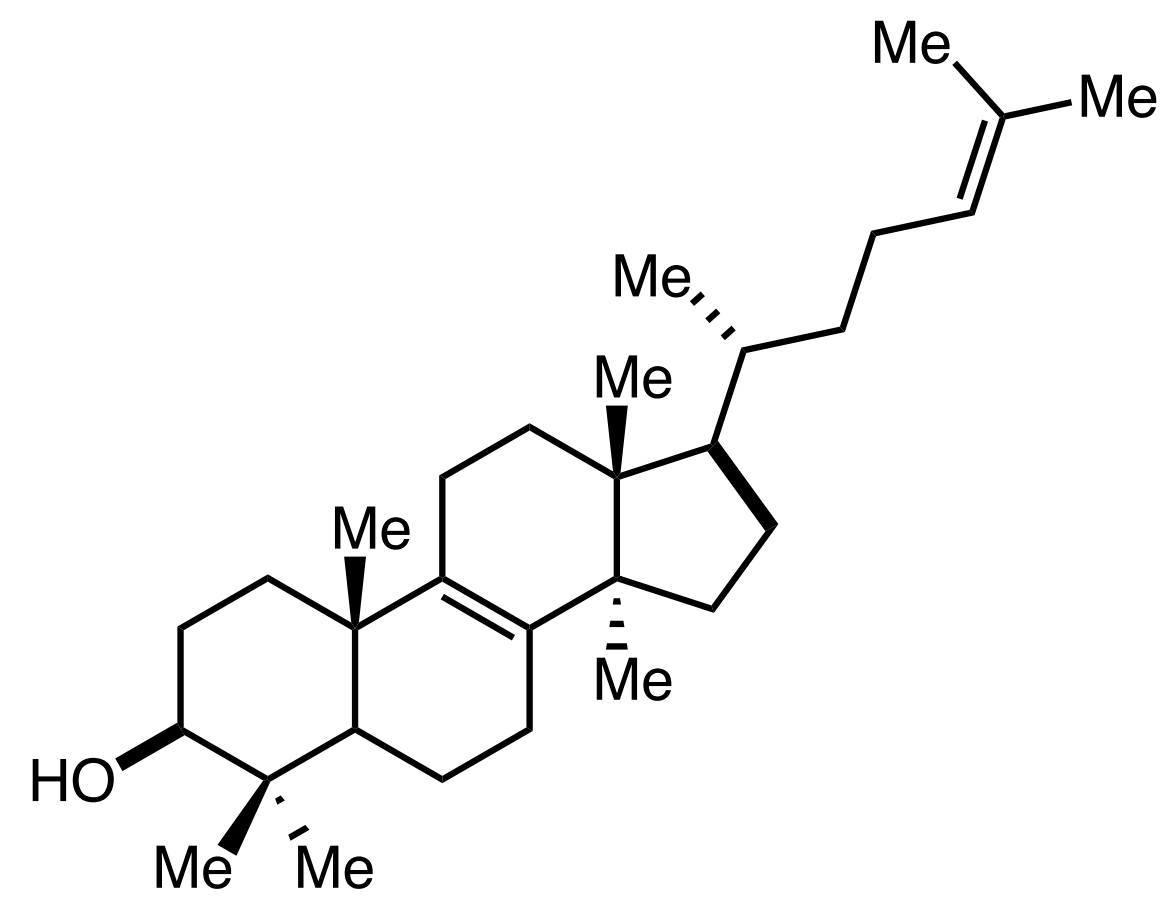
Azole Target – Ergosterol Biosynthesis



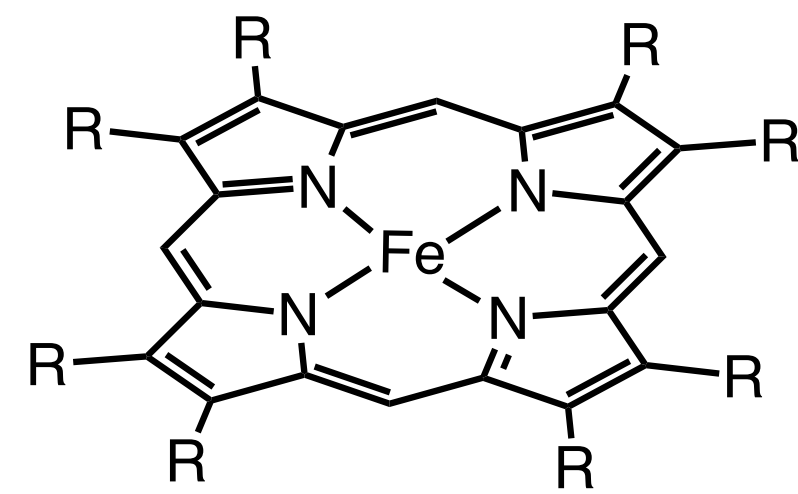
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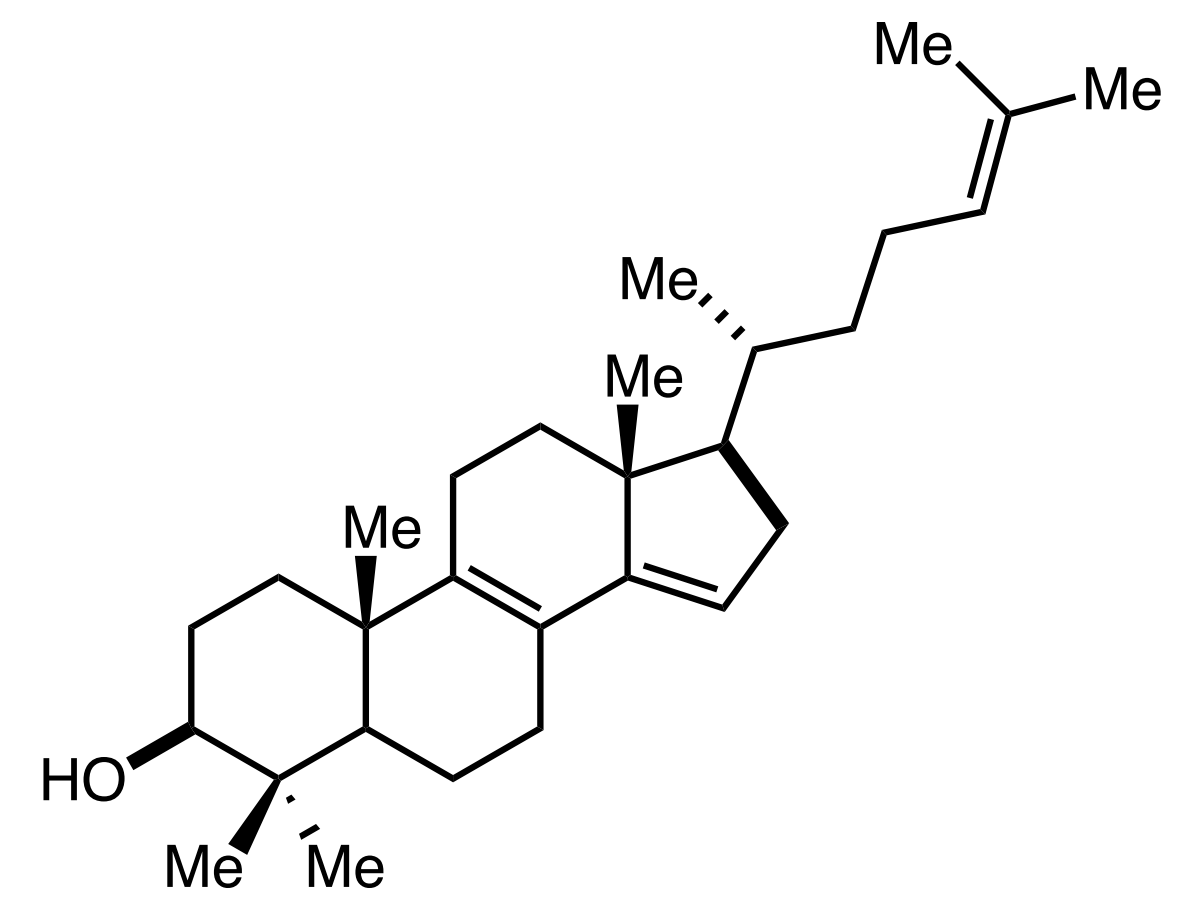
Azole Target – Ergosterol Biosynthesis



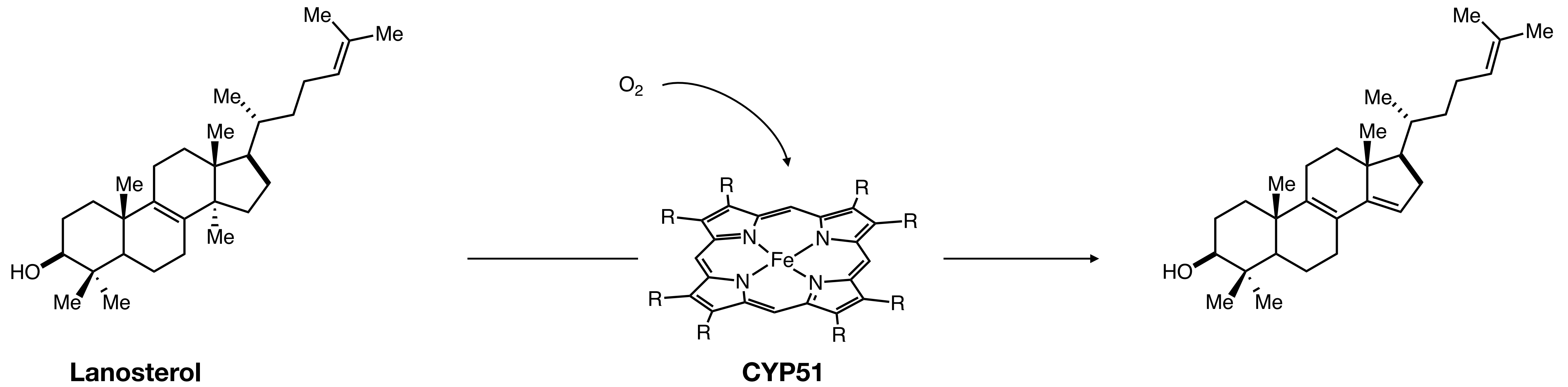
Lanosterol



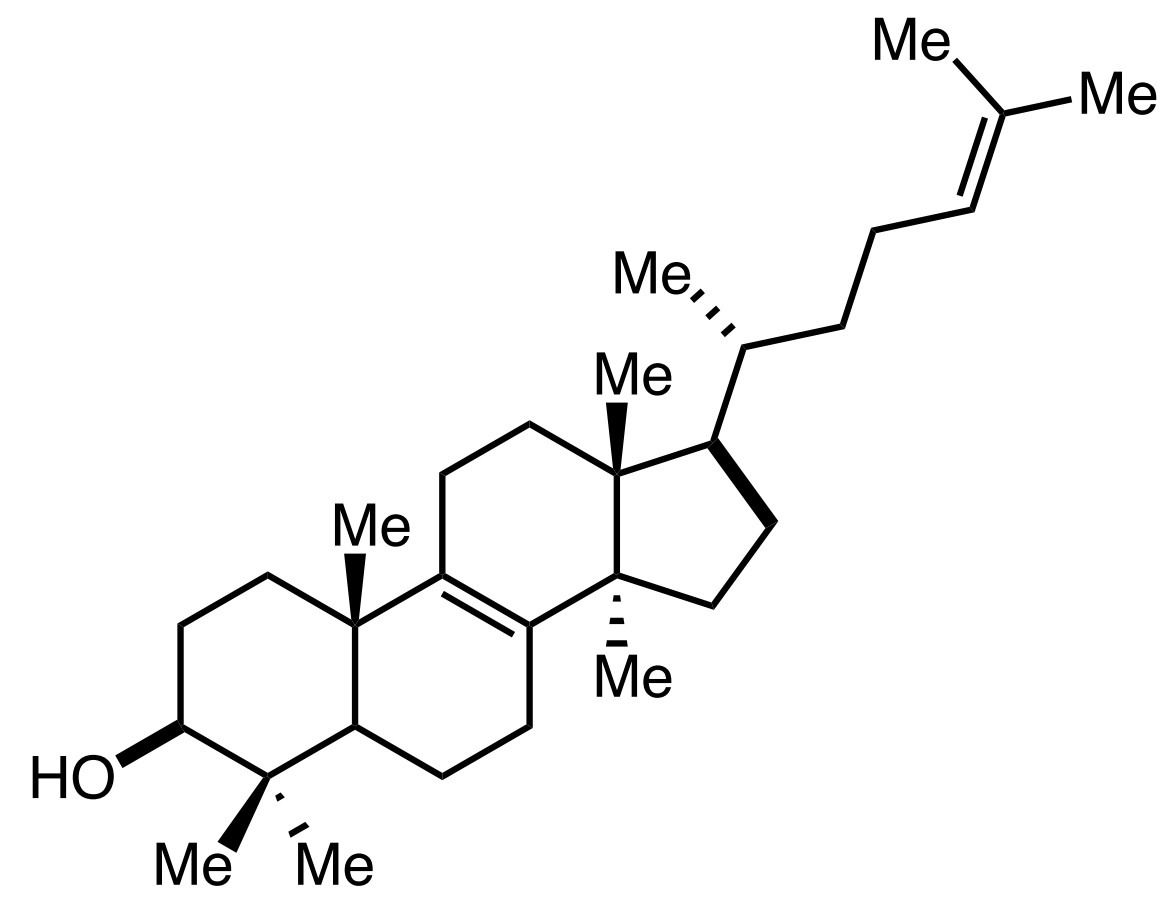
CYP51



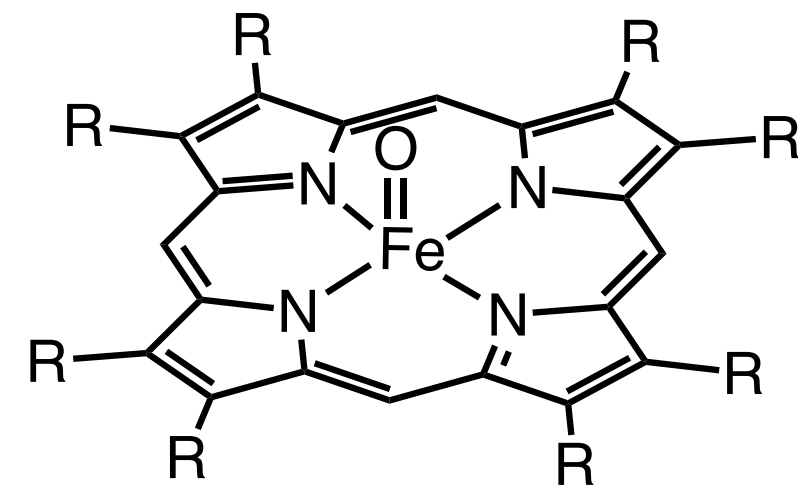
Azole Target – Ergosterol Biosynthesis



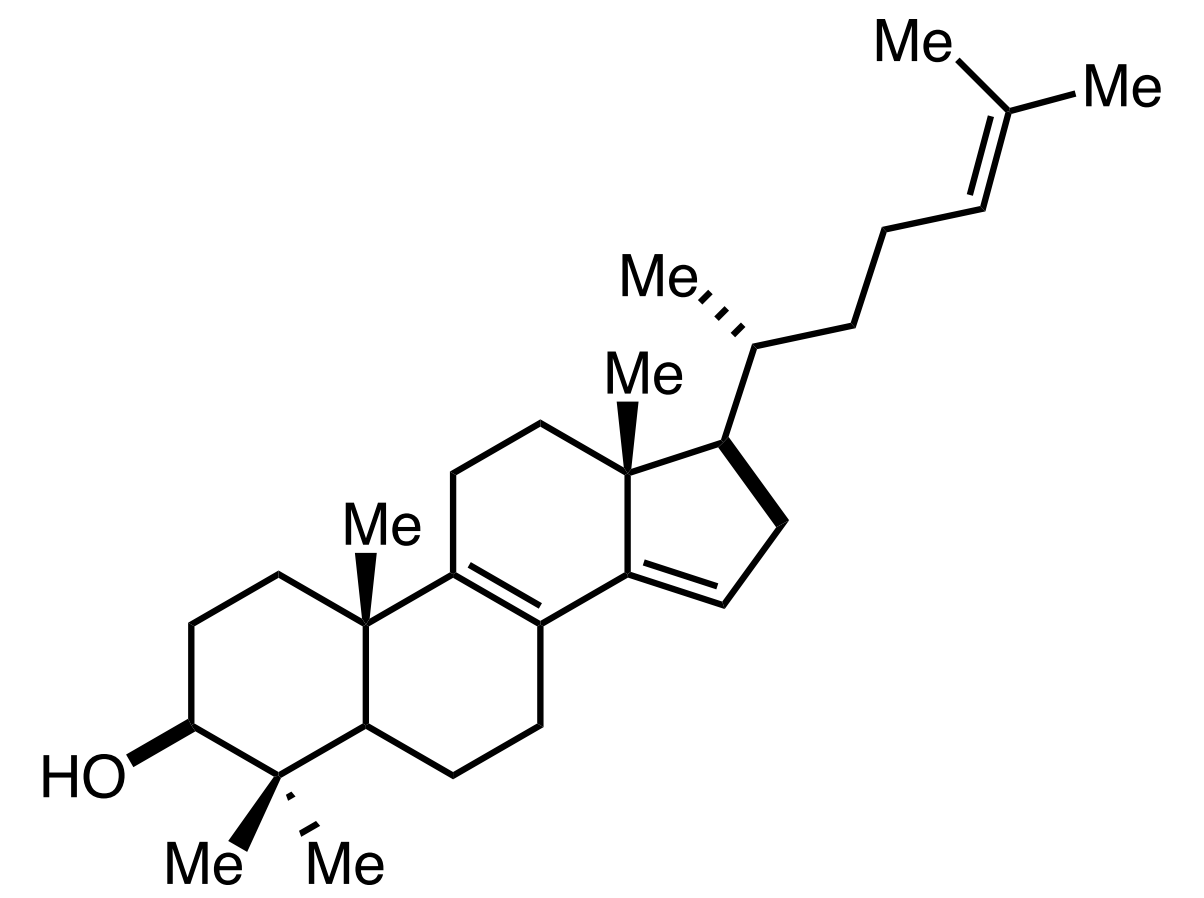
Azole Target – Ergosterol Biosynthesis



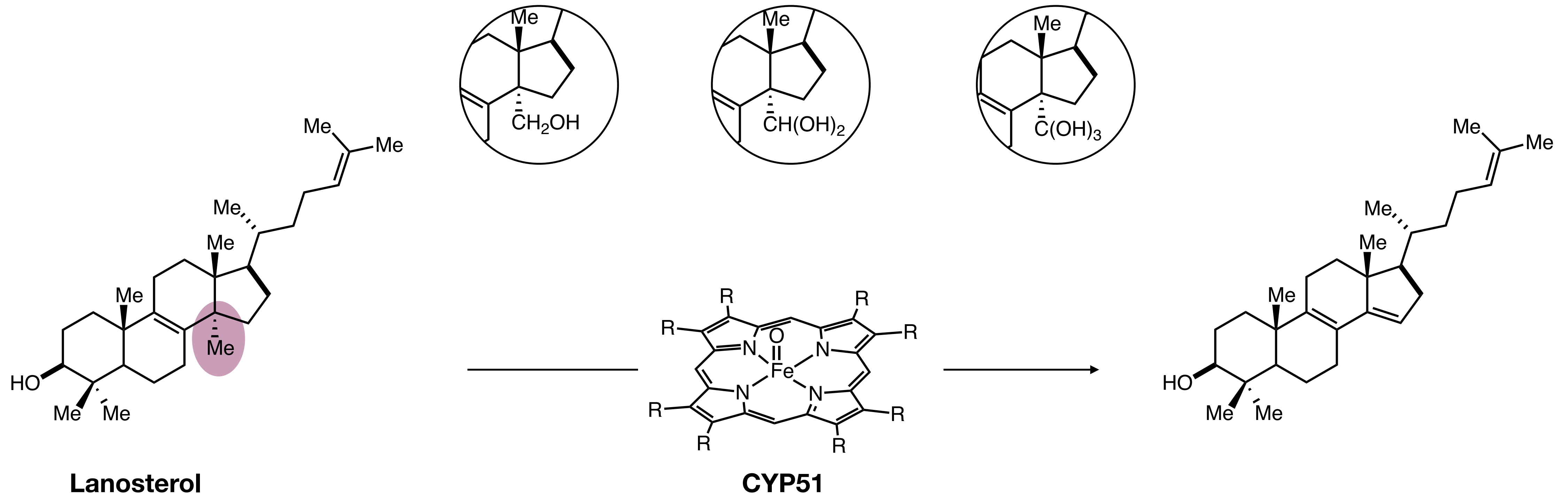
Lanosterol



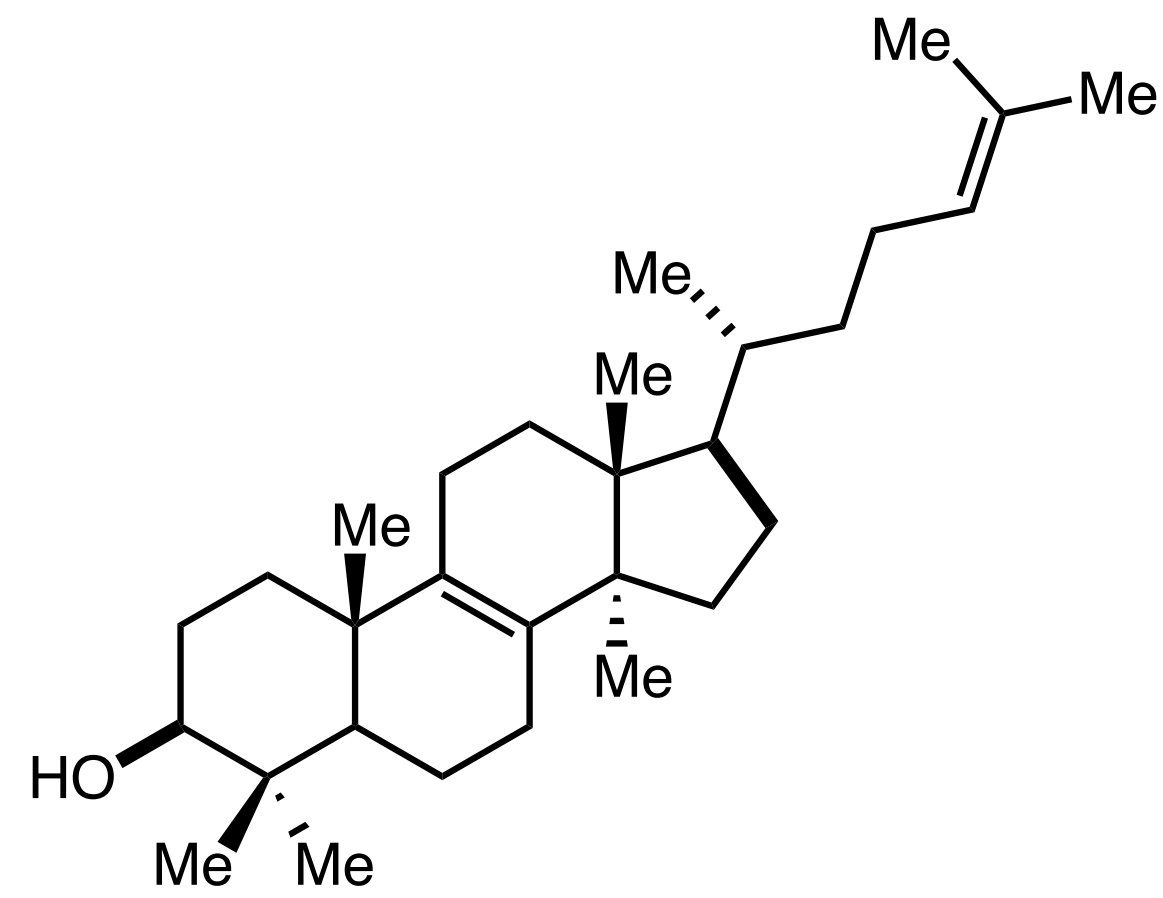
CYP51



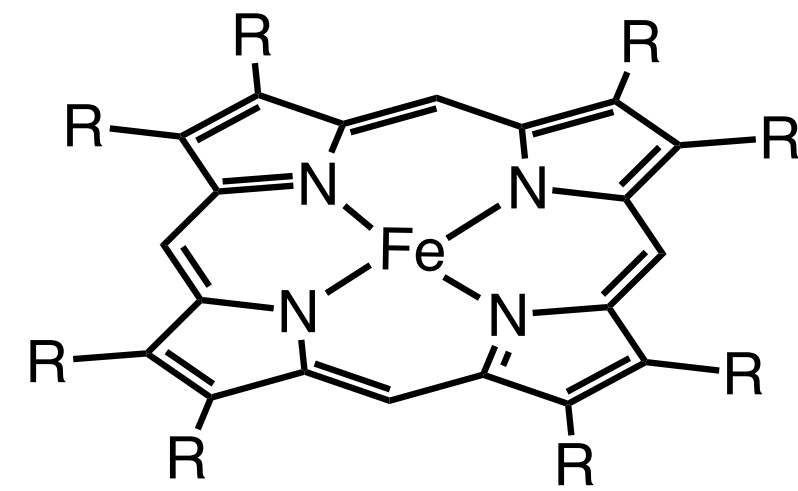
Azole Target – Ergosterol Biosynthesis



Azole Target – Ergosterol Biosynthesis



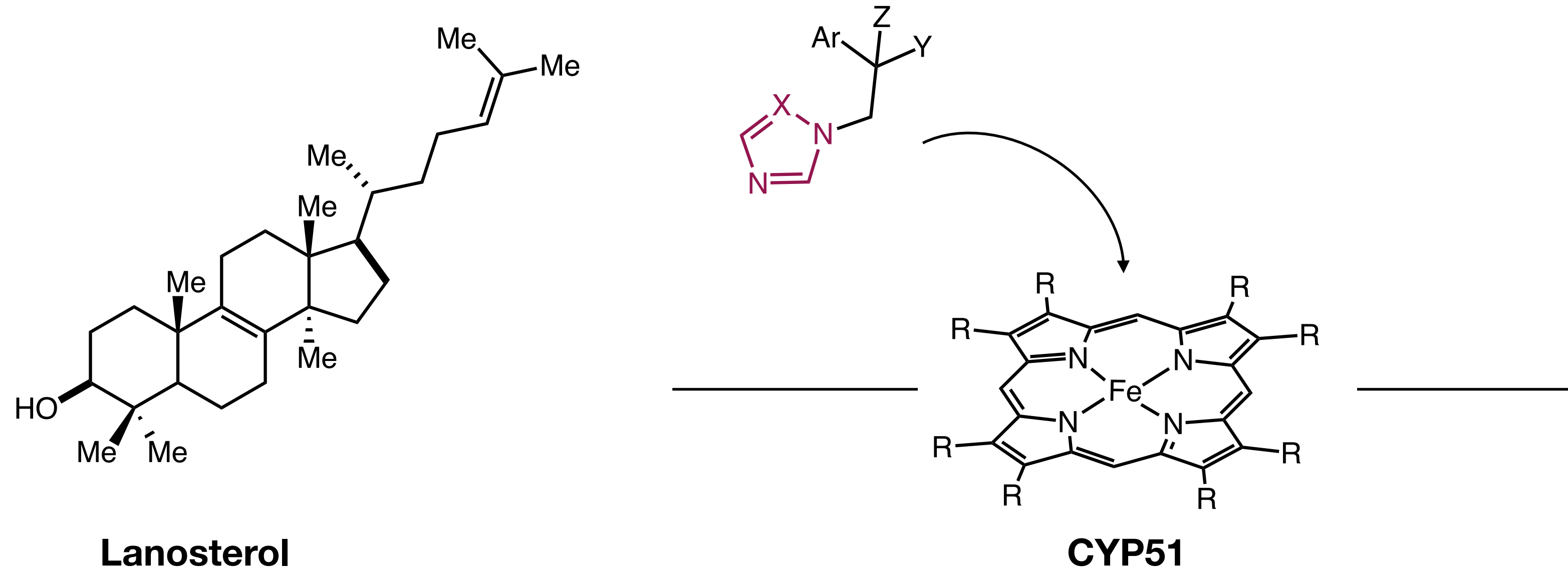
Lanosterol



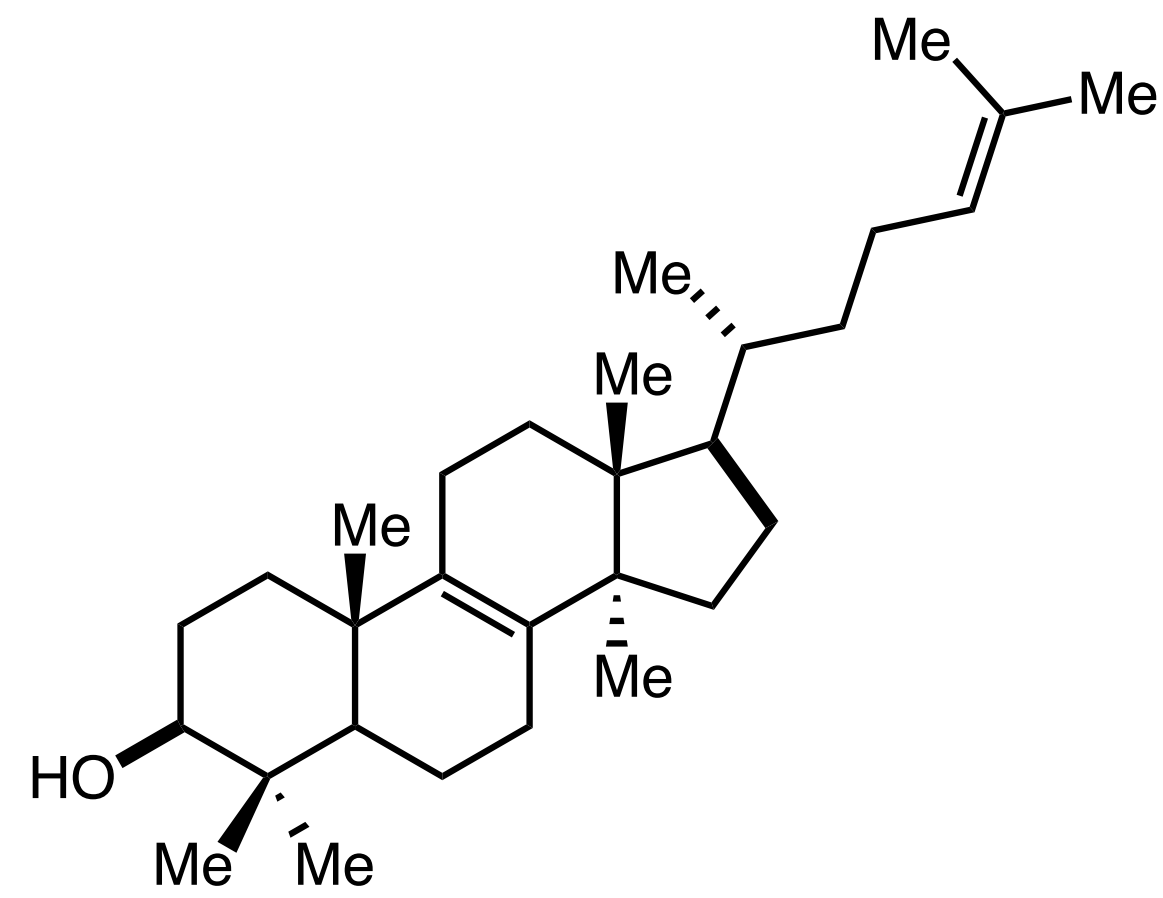
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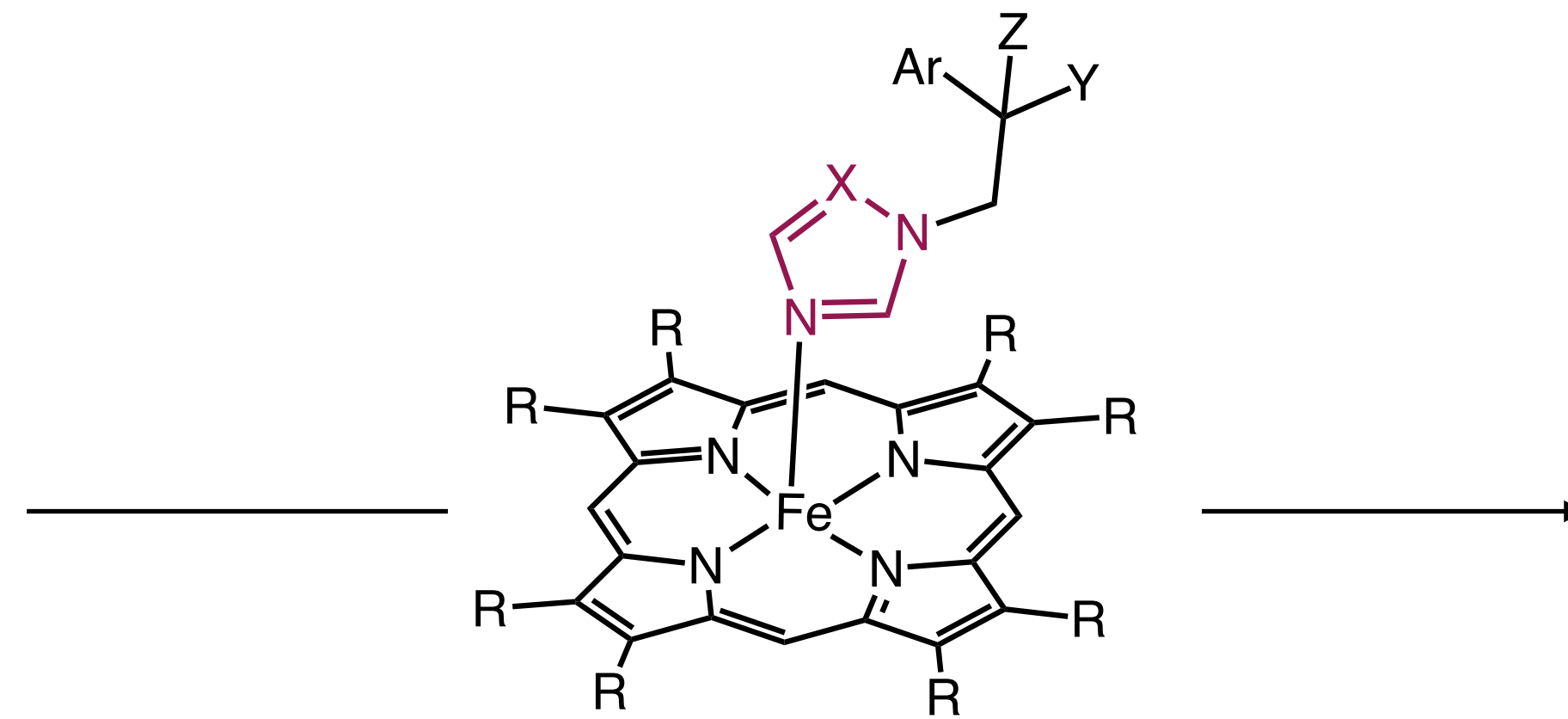
Azole Target – Ergosterol Biosynthesis



Azole Target – Ergosterol Biosynthesis

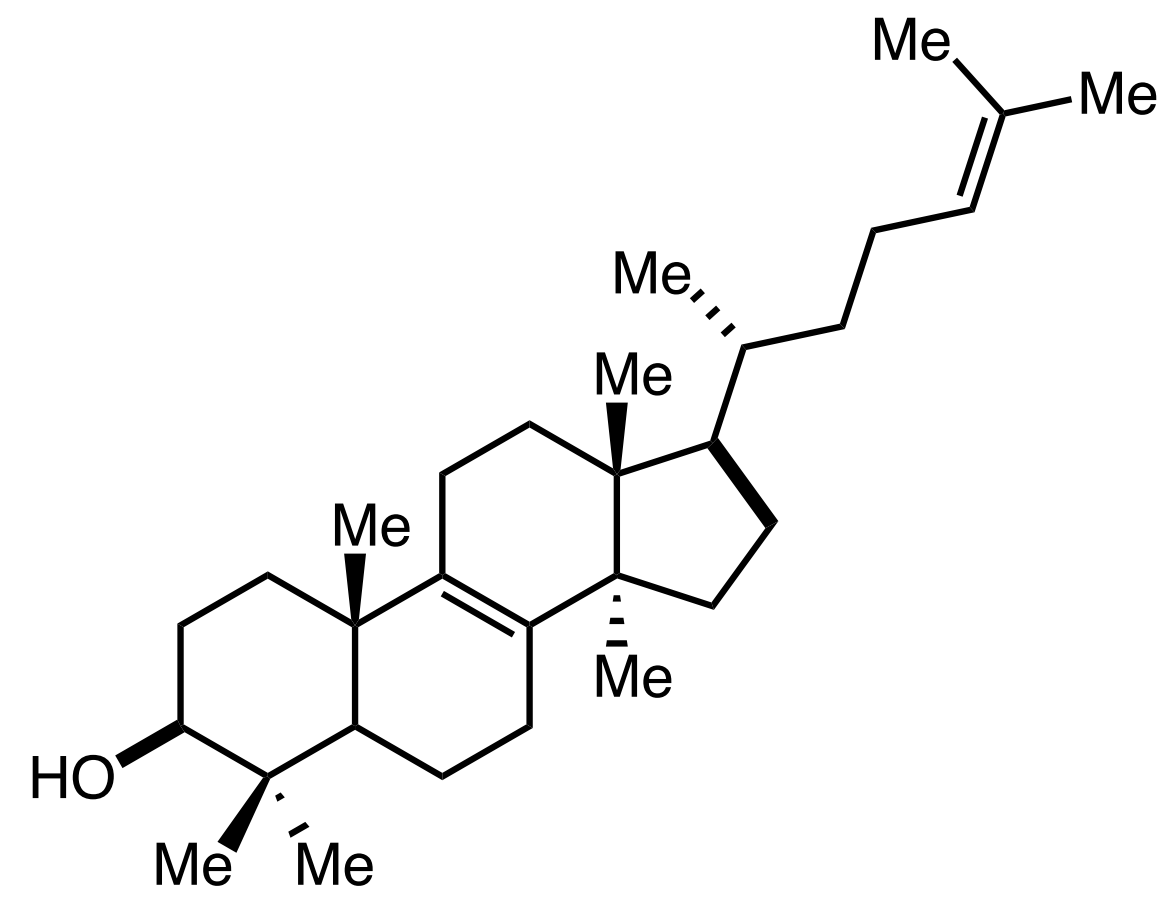


Lanosterol

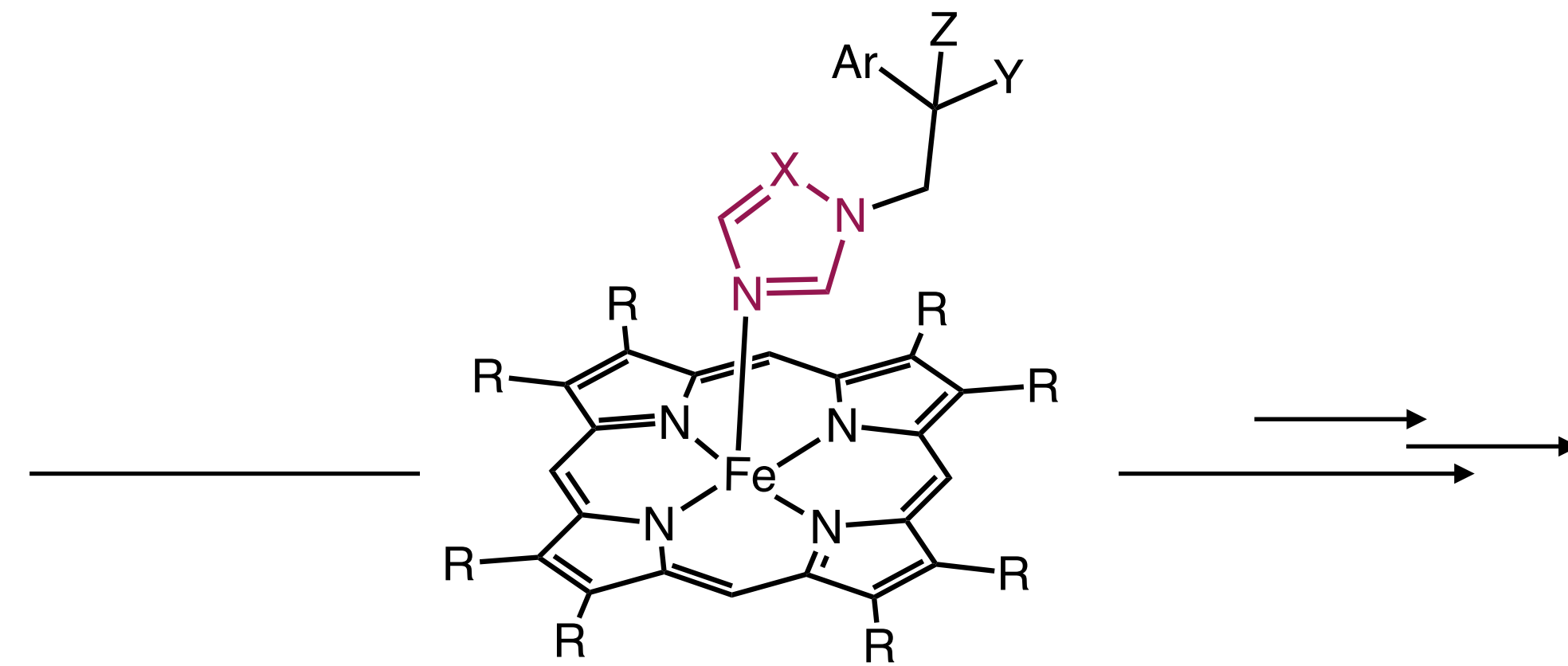


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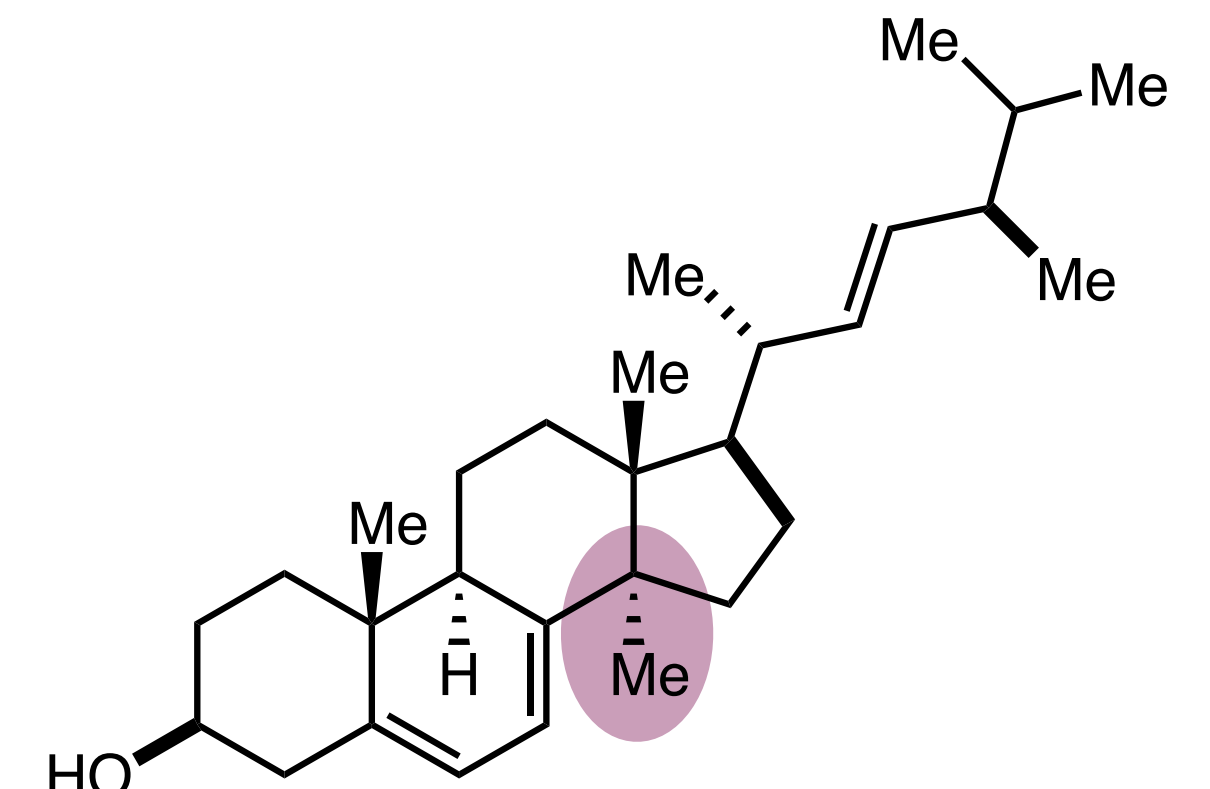
Azole Target – Ergosterol Biosynthesis



Lanosterol



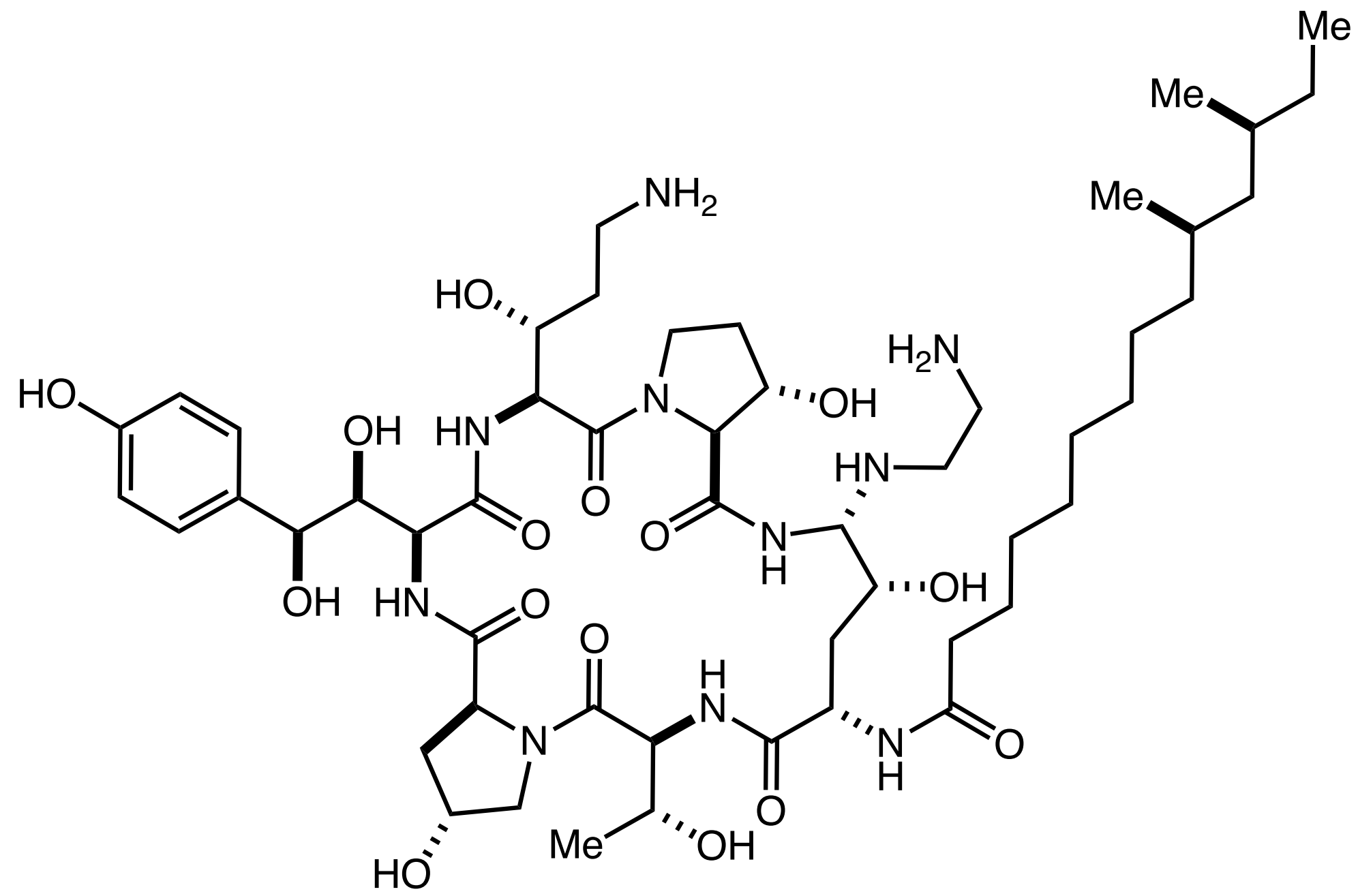
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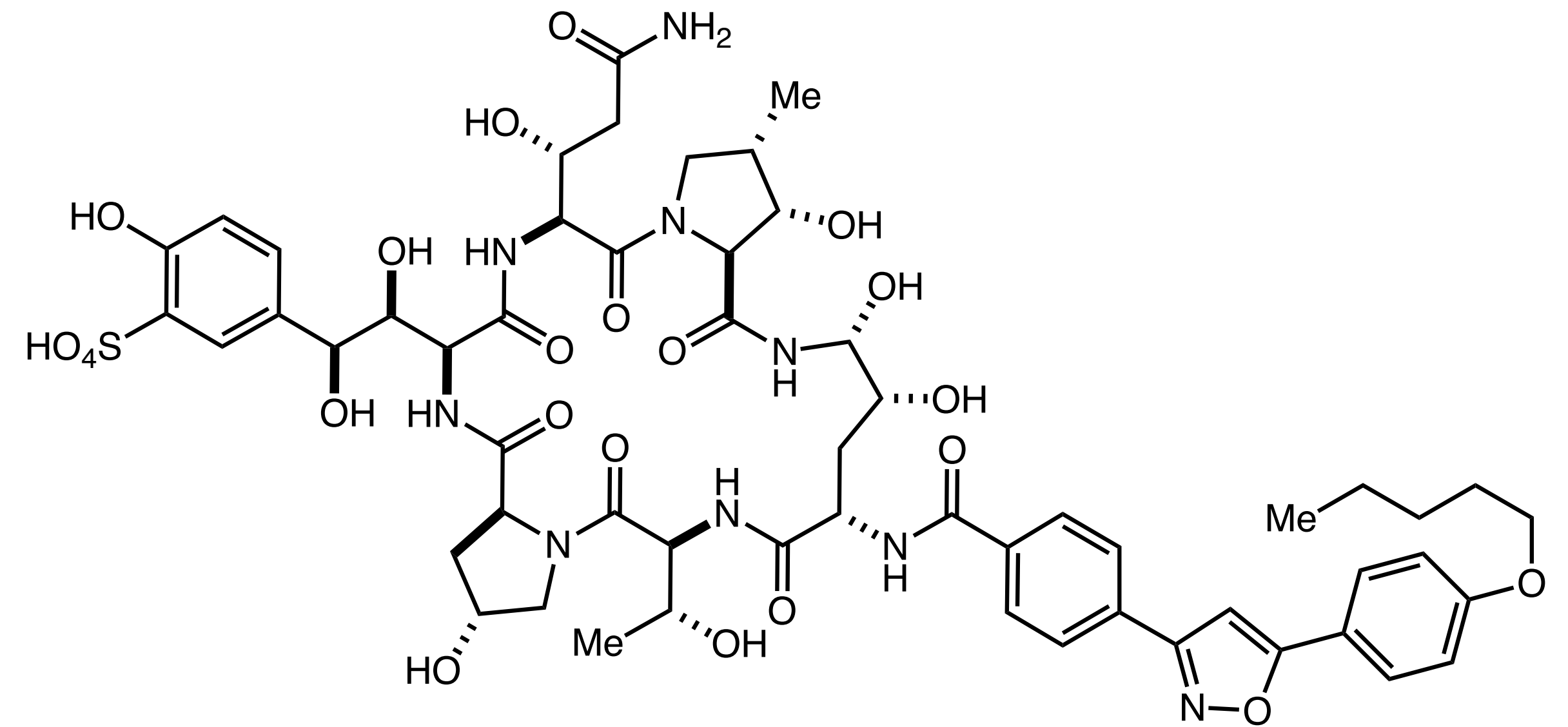
α -methyl Ergosterol

toxic to fungi, cell membrane deformed

Echinocandins

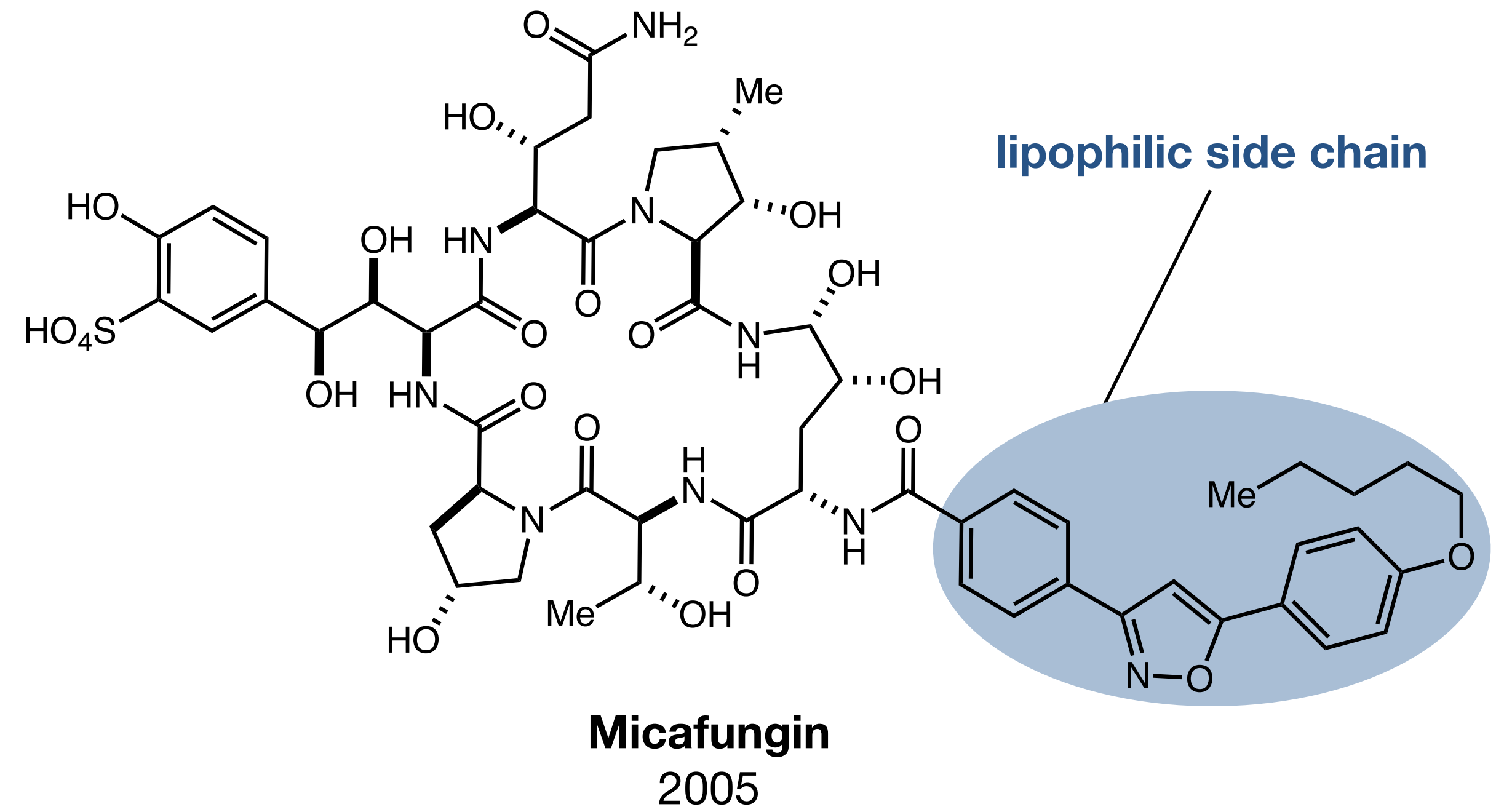
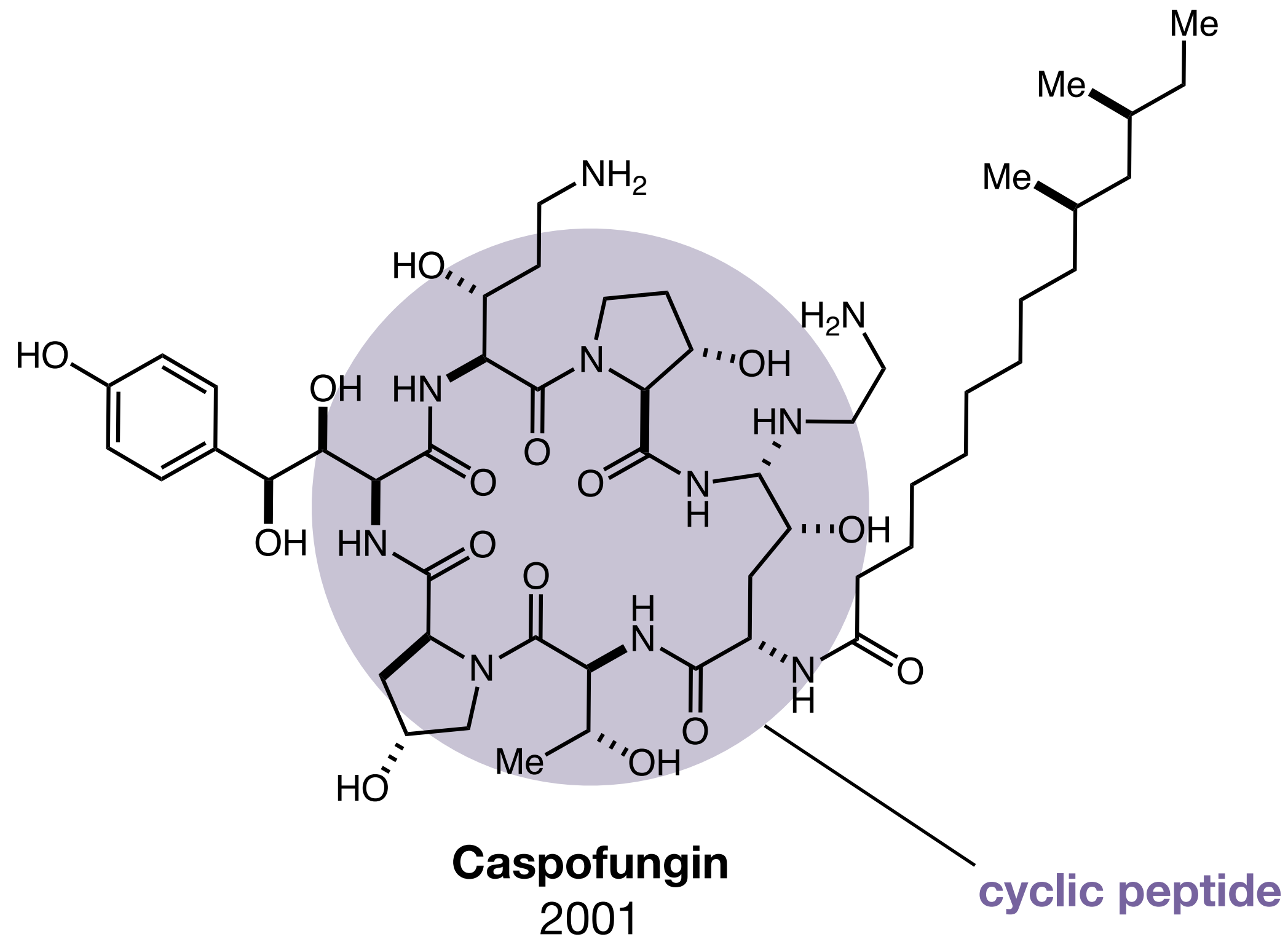


Caspofungin
2001

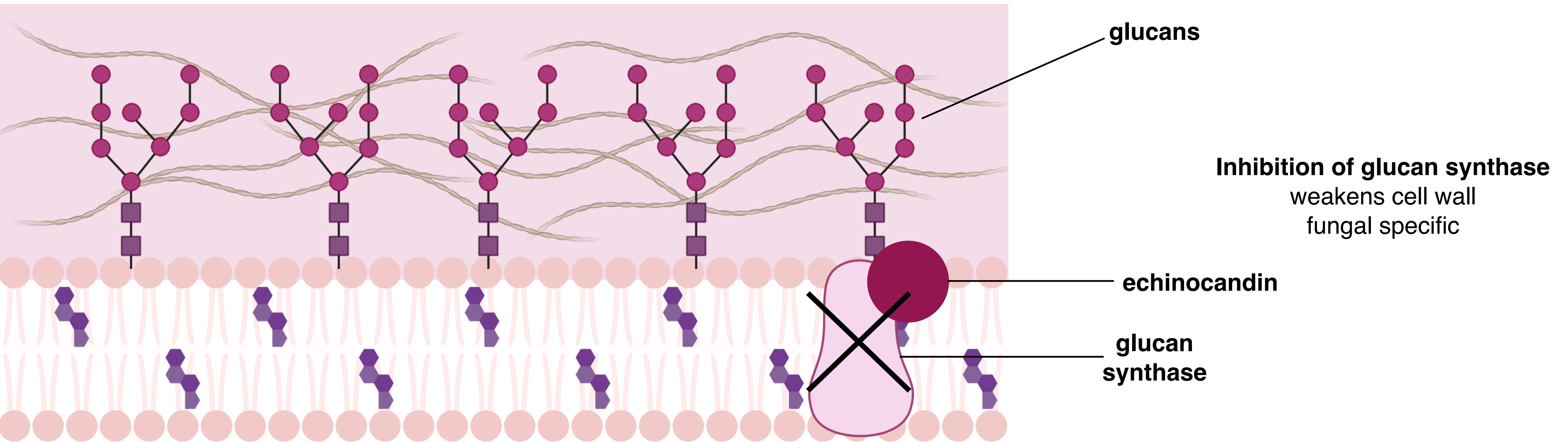


Micafungin
2005

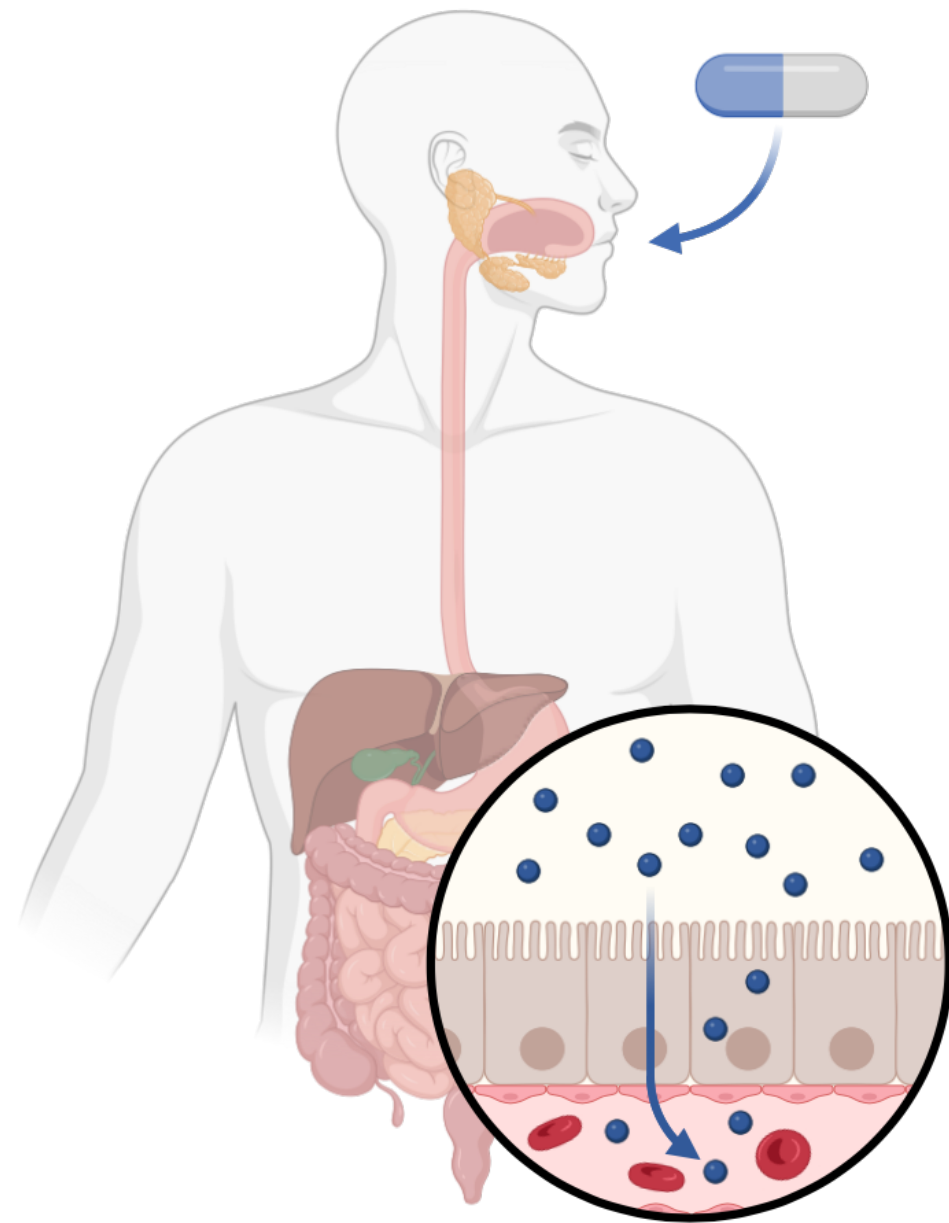
Echinocandins



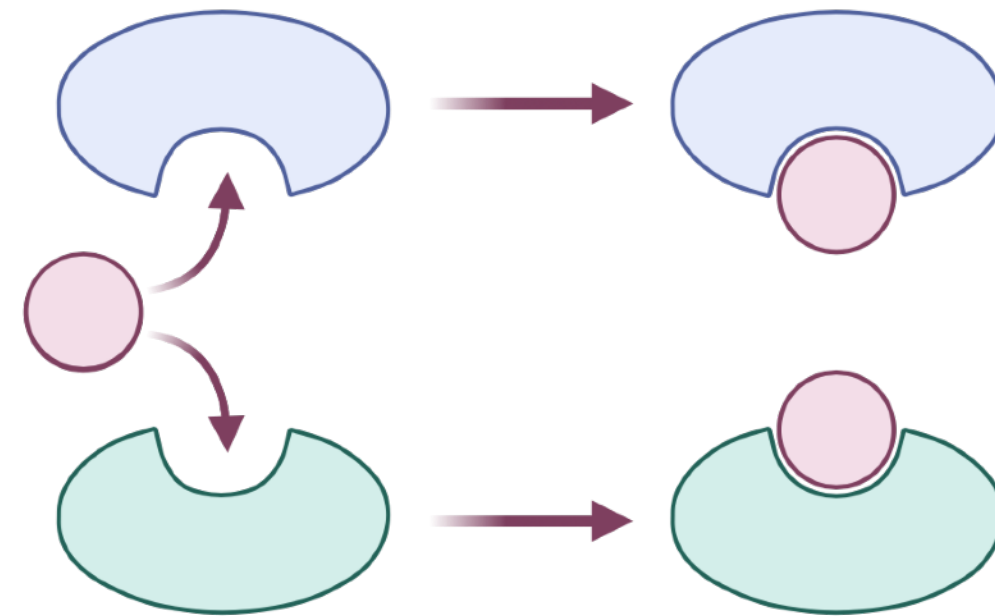
Echinocandins – Mechanism of Action



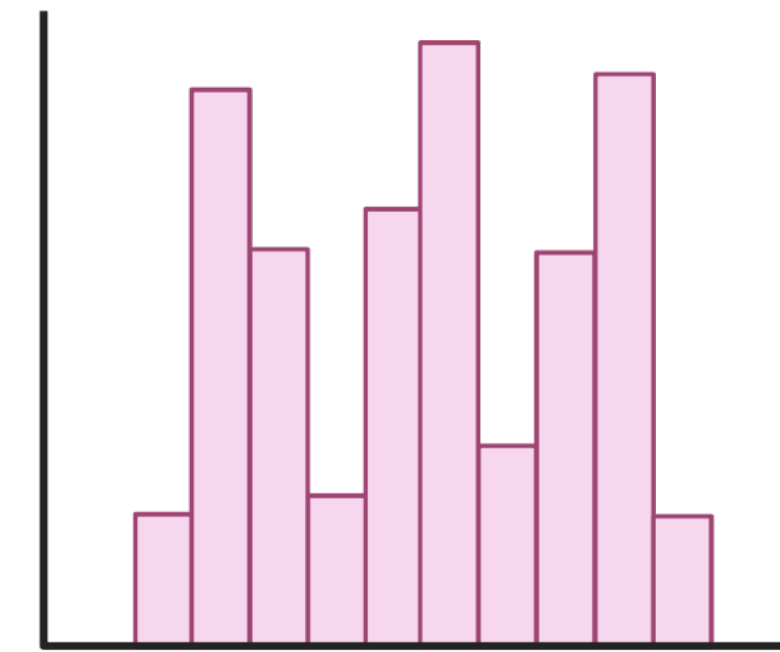
Drawbacks



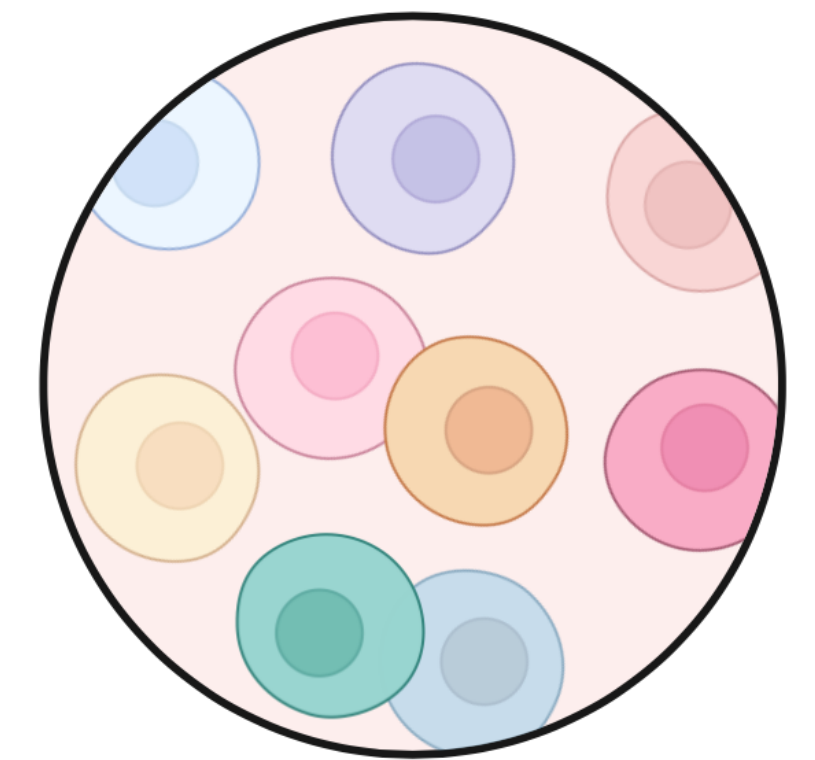
Poor Oral Bioavailability
echinocandins, polyenes



Non-Specific Binding
azoles, polyenes



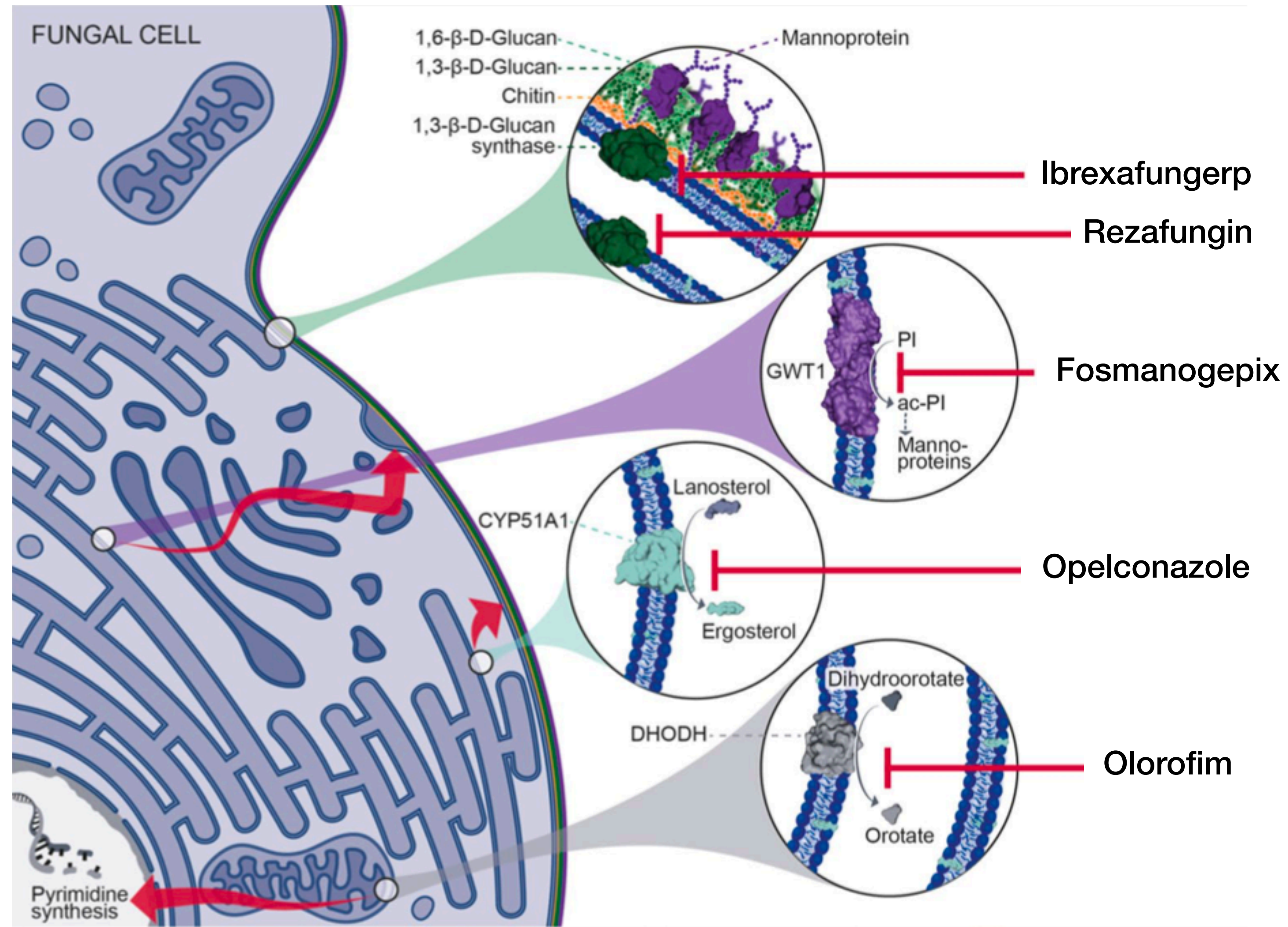
Strain-Variable Activity
all classes



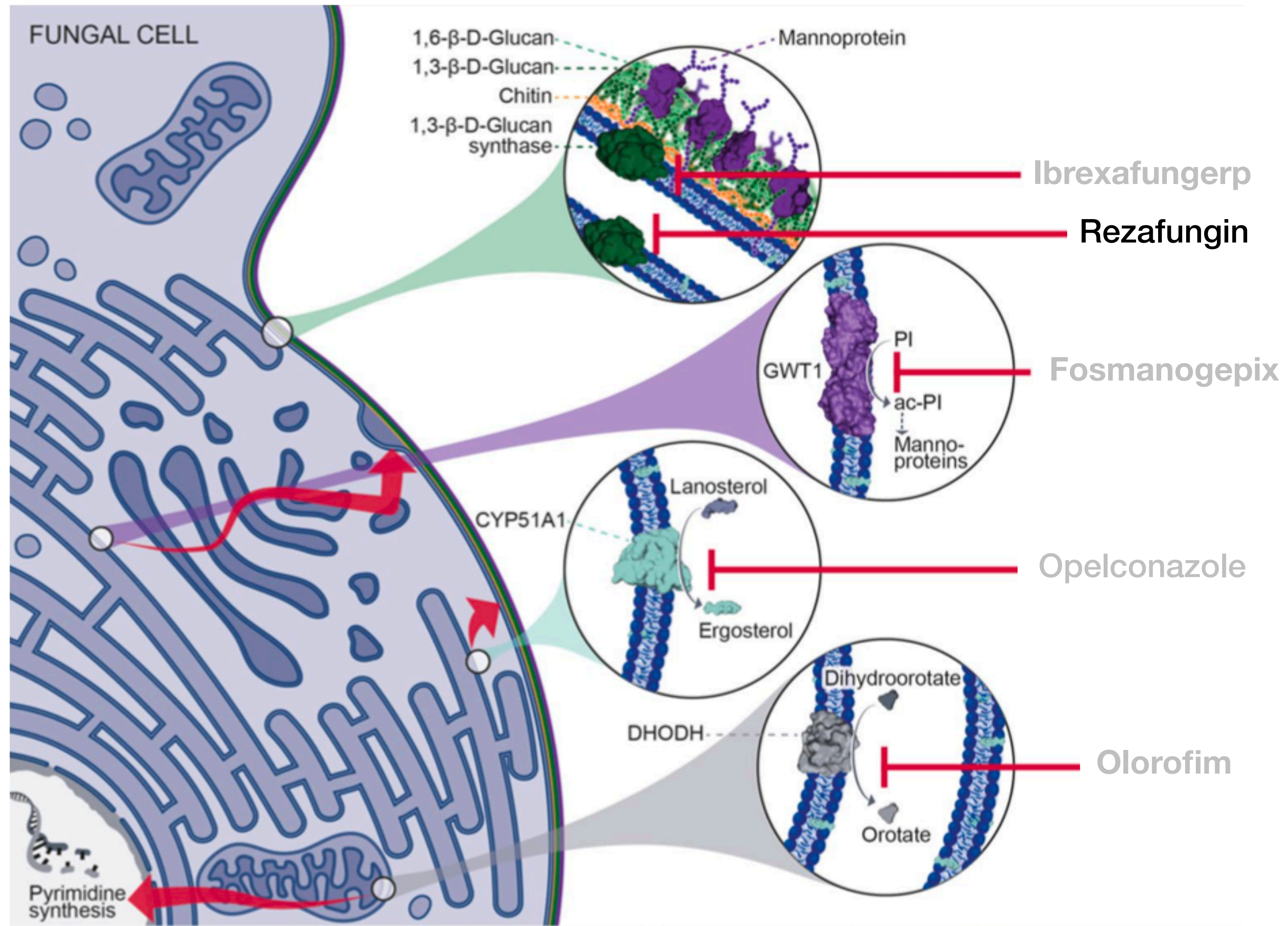
Drug Resistant Strains
emerging problem

the development of novel antifungals is essential to combat these issues

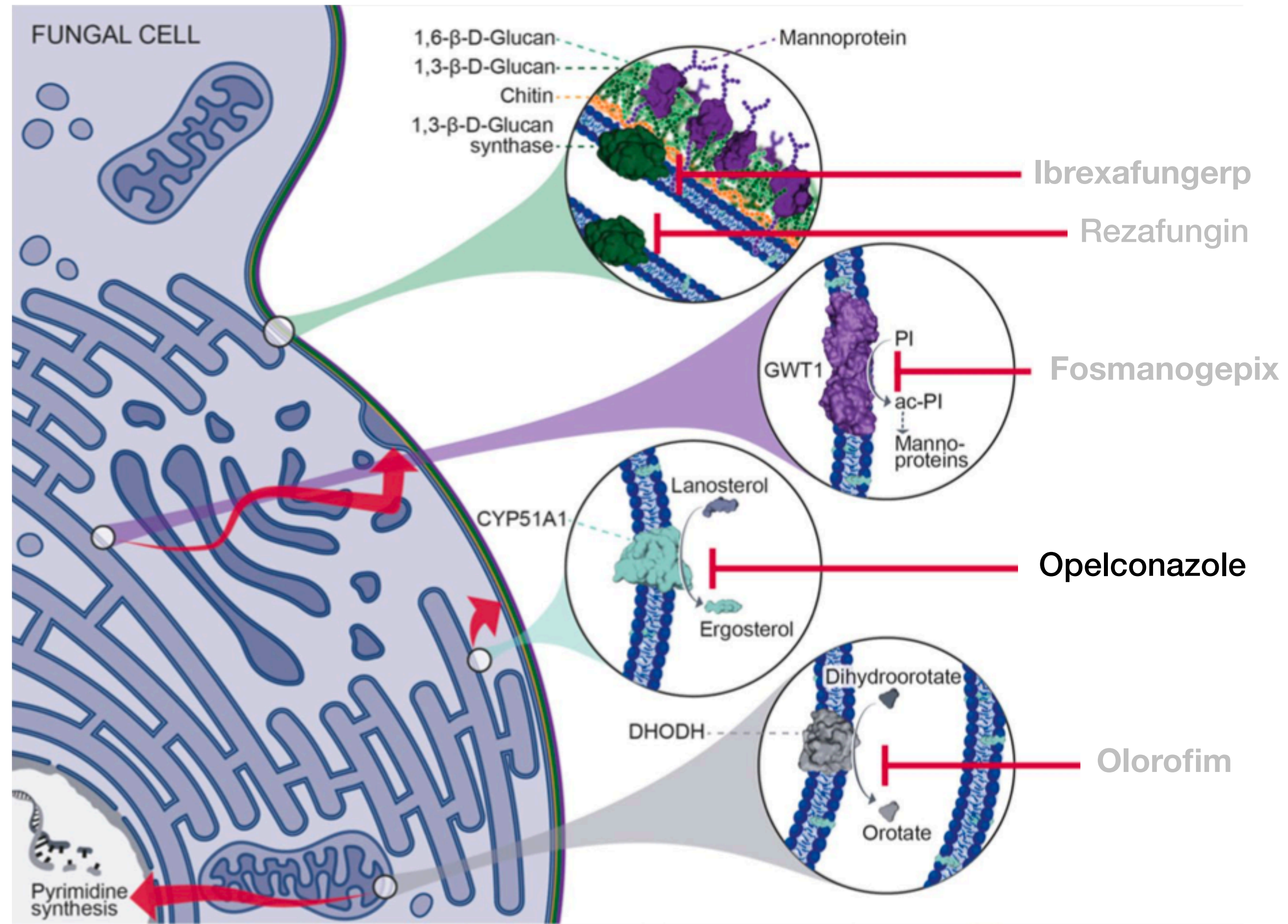
Novel Drugs, Novel Mechanisms, Novel Delivery



Novel Drugs, Novel Mechanisms, Novel Delivery



Novel Drugs, Novel Mechanisms, **Novel Delivery**



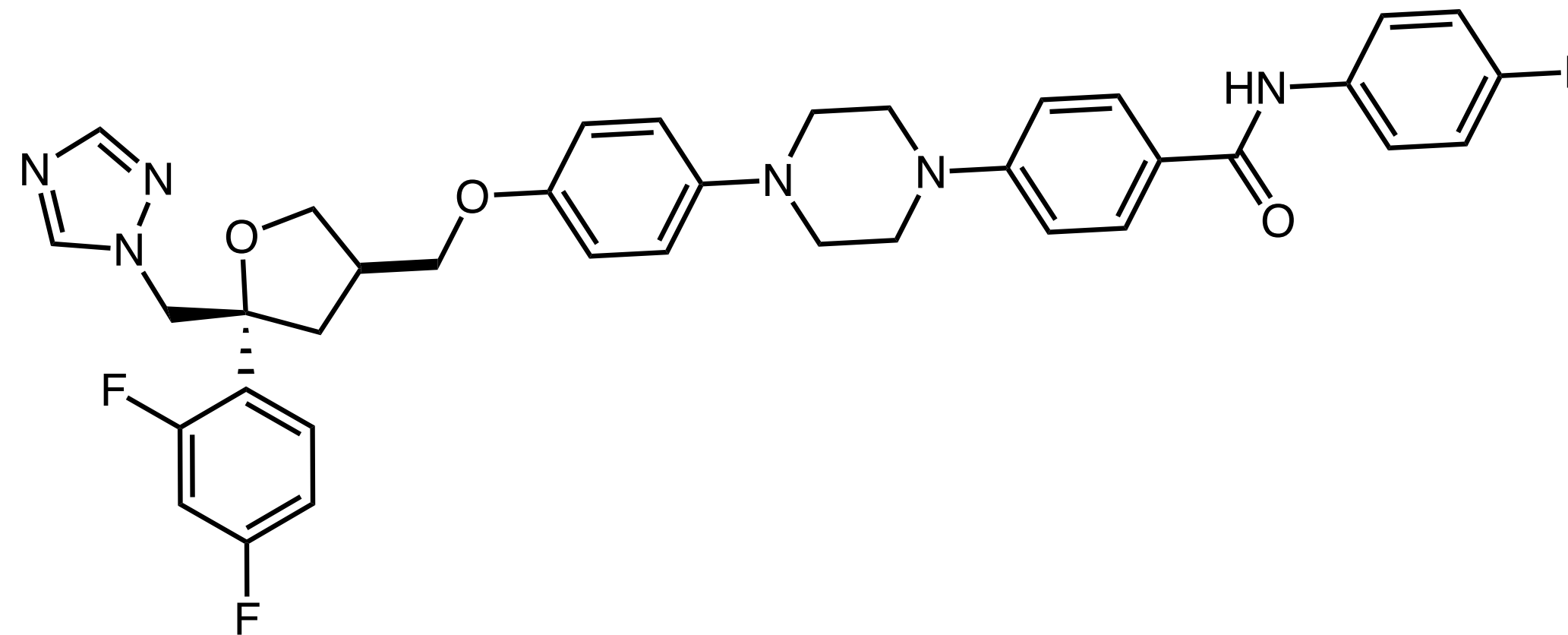
Opelconazole – Pulmocide



PULMOCIDE
INHALED RESPIRATORY MEDICINE



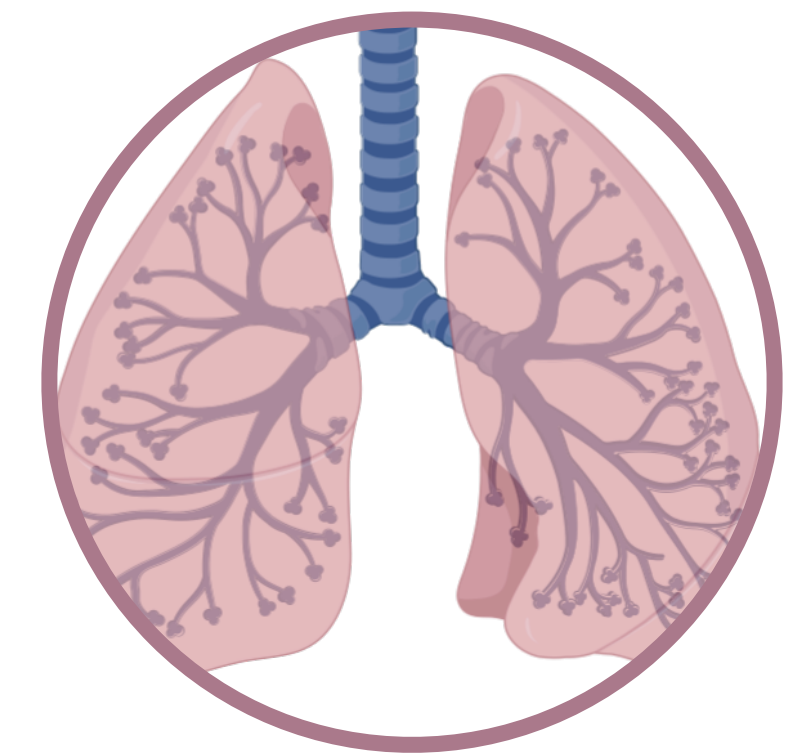
Aspergillosis
usually lung localized



significantly increased potency
improvement over standard care



designed for inhalation
first triazole of this design



lung retention
low systemic exposure

<https://pulmocide.com/opelconazole/>

Pagani, N.; Armstrong-James, D.; Reed, A. *J. Heart Lung Transplant.* **2020**, *39*(12), 1505–1506.

Opelconazole – Pulmocide

***Aspergillus Fumigatus* in lung transplant patients**

<https://pulmocide.com/opelconazole/>

Pagani, N.; Armstrong-James, D.; Reed, A. *J. Heart Lung Transplant.* **2020**, *39*(12), 1505–1506.

Opelconazole – Pulmocide

***Aspergillus Fumigatus* in lung transplant patients**

Patient 1



pre-treatment

Patient 2

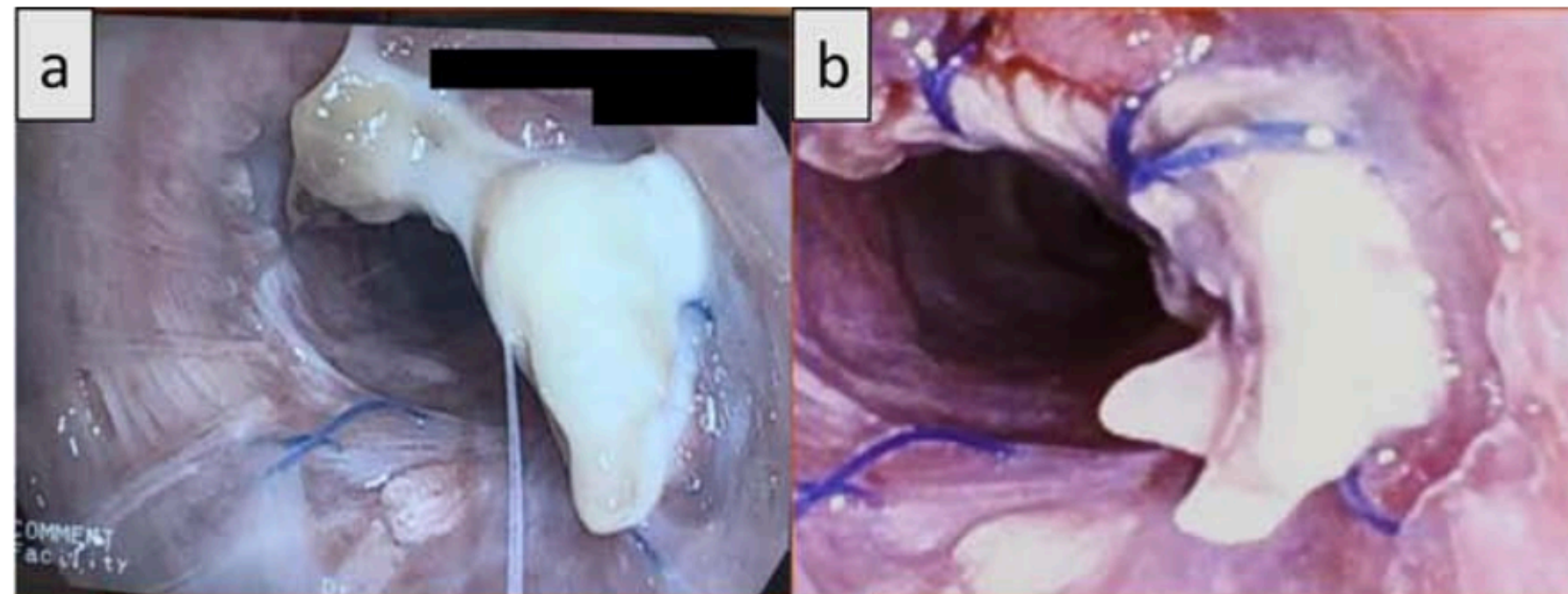


pre-treatment

Opelconazole – Pulmocide

***Aspergillus Fumigatus* in lung transplant patients**

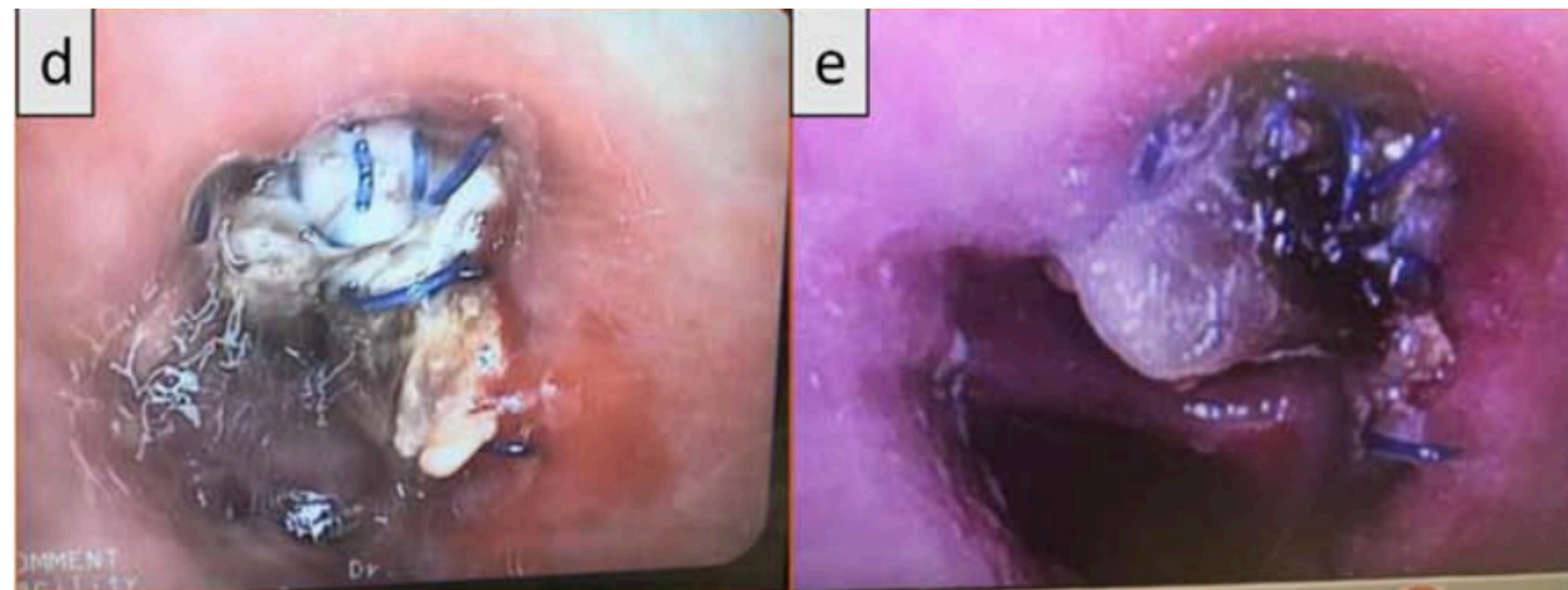
Patient 1



pre-treatment

2 weeks treatment

Patient 2



pre-treatment

2 weeks treatment

<https://pulmocide.com/opelconazole/>

Opelconazole – Pulmocide

***Aspergillus Fumigatus* in lung transplant patients**

Patient 1

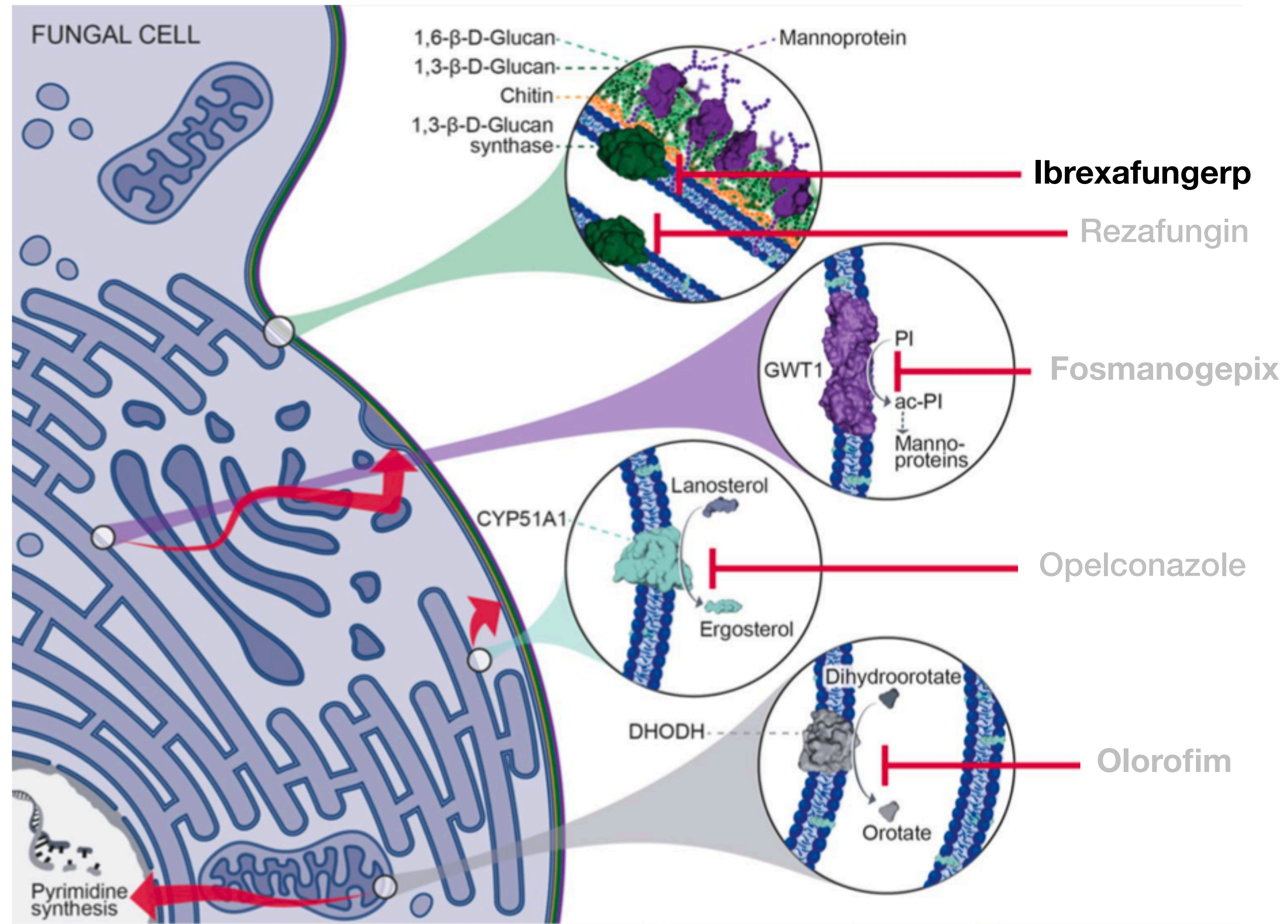


Patient 2



<https://pulmocide.com/opelconazole/>

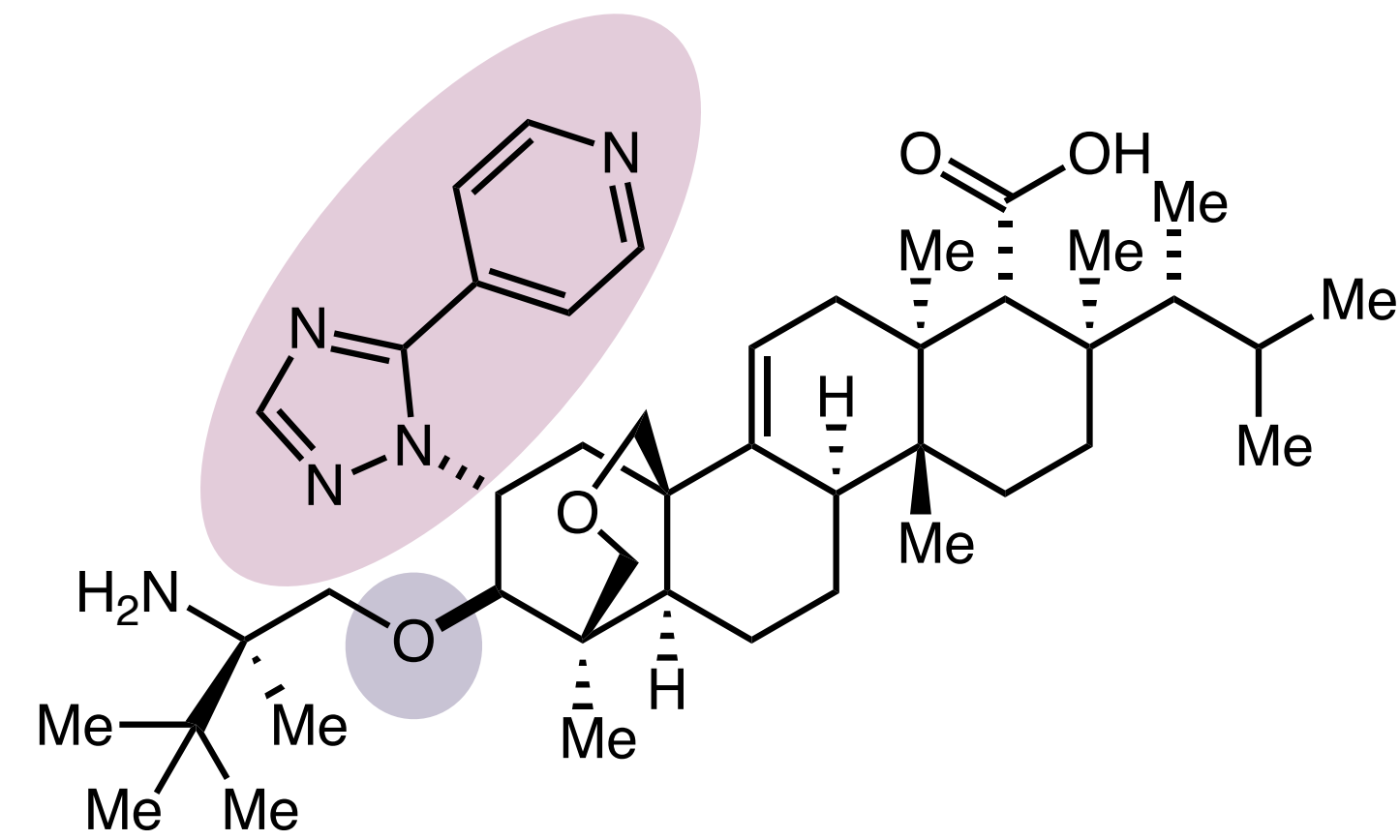
Novel Drugs, Novel Mechanisms, Novel Delivery



Ibrexafungerp – Scynexis

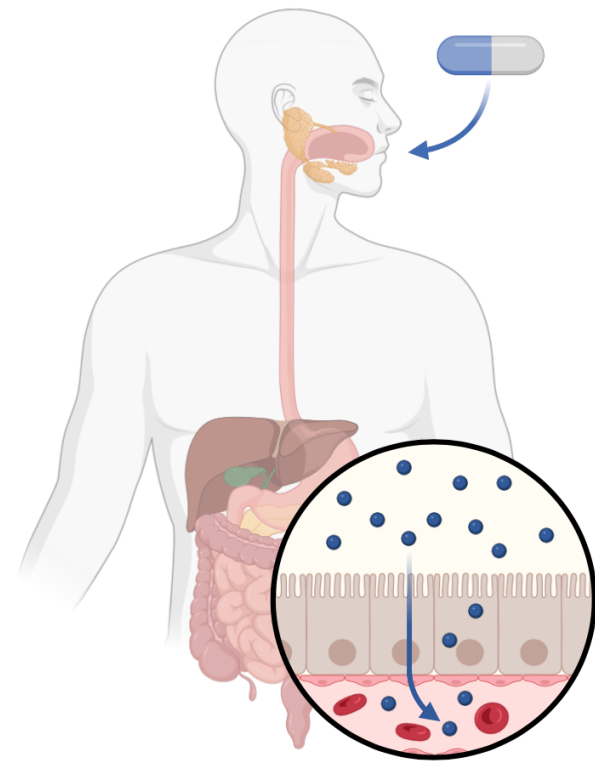


**first non-azole oral treatment
for yeast infections**

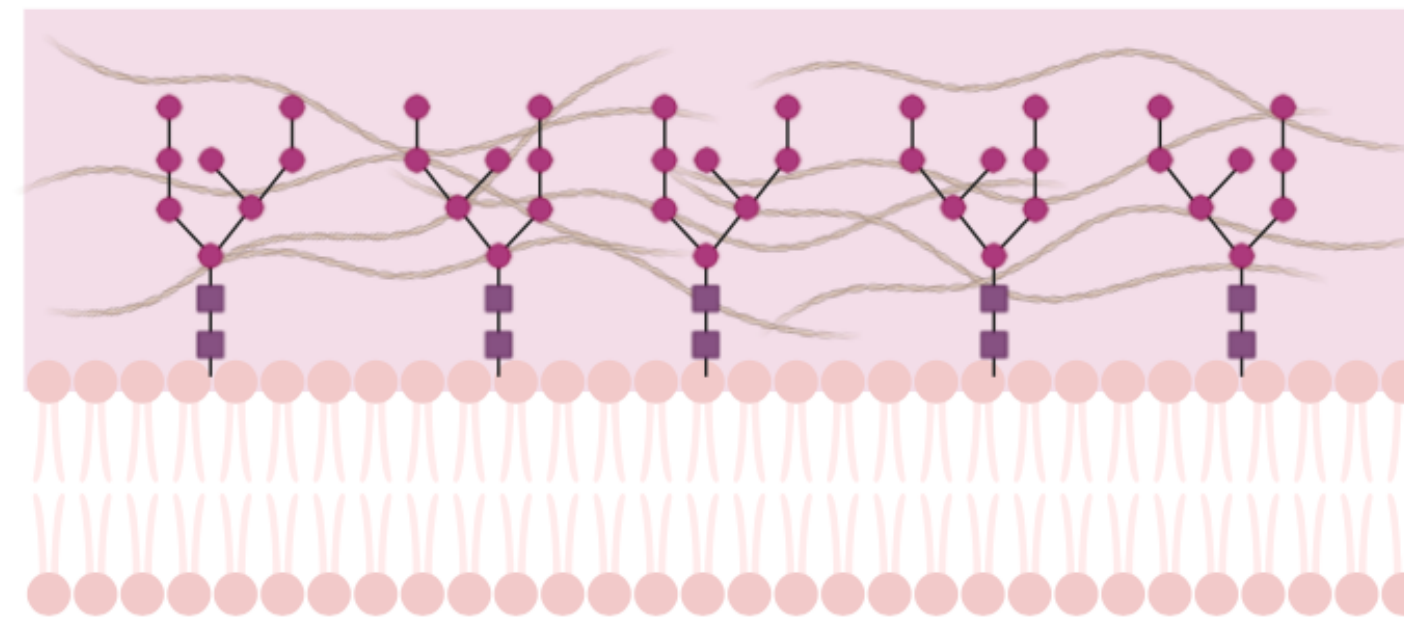


**Triterpenoid – First in class
2021**

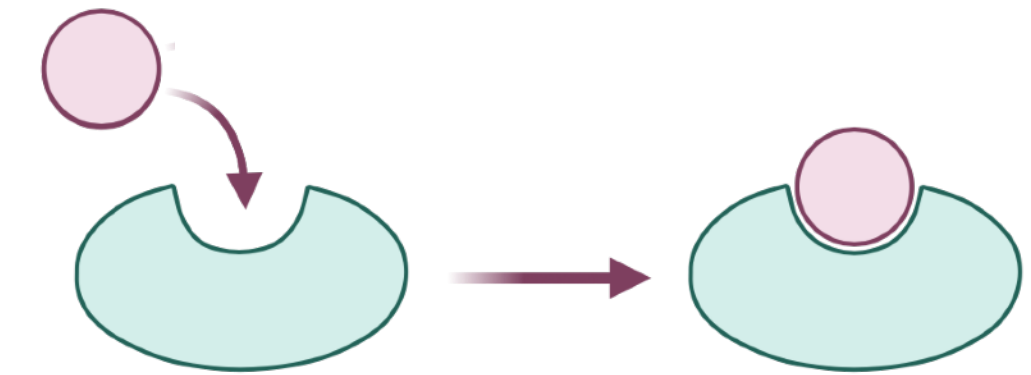
Ibrexafungerp – Scynexis



high bioavailability
oral and IV administration



disruption of cell wall
similar mechanism to echinocandins
limited off-target effects



novel binding site
activity against echinocandin-
and azole-resistant strains

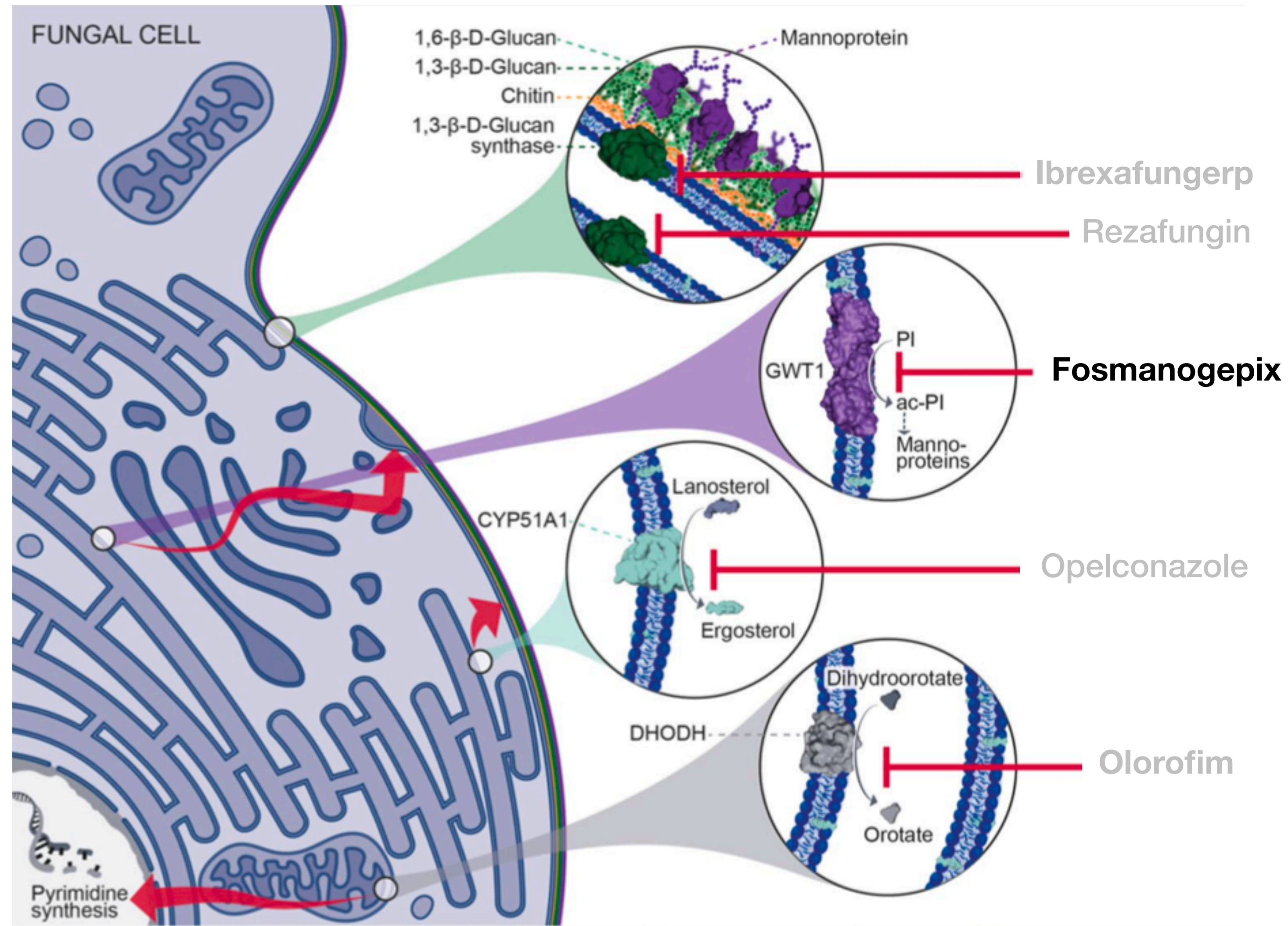
GSK collaboration for IV formulation in clinical trials

Phillips, N. A.; Rocktashel, M.; Merjanian, L. *Drug Des. Devel. Ther.* **2023**, *17*, 363–367.

Davis, M. R.; Donnelley, M. A.; Thompson, G.R. *Med. Mycol.* **2020**, *58*(5), 579–592.

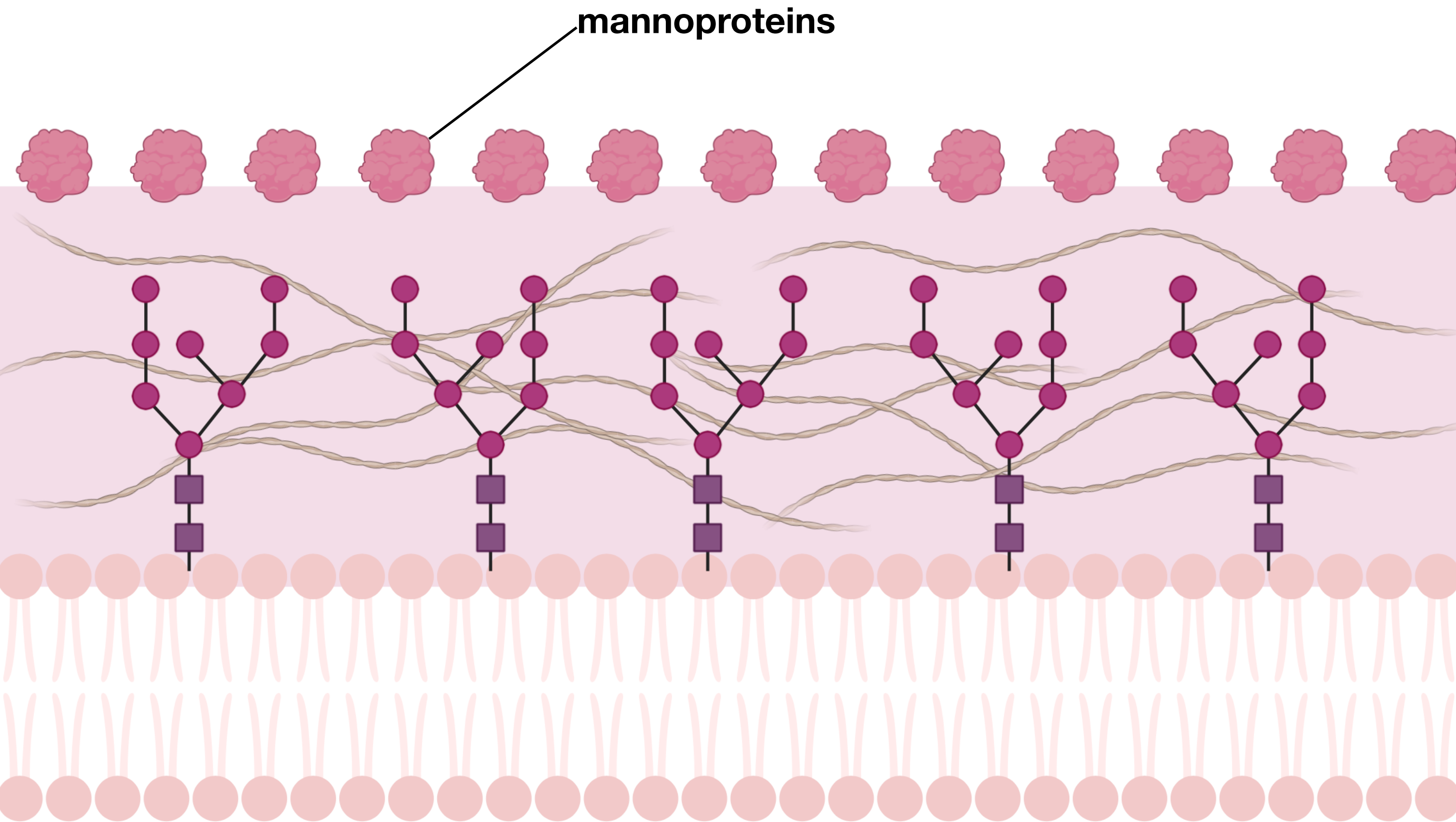
Jallow, S.; Govender, N. P. *J. Fungi.* **2021**, *7*, 163.

Novel Drugs, Novel Mechanisms, Novel Delivery



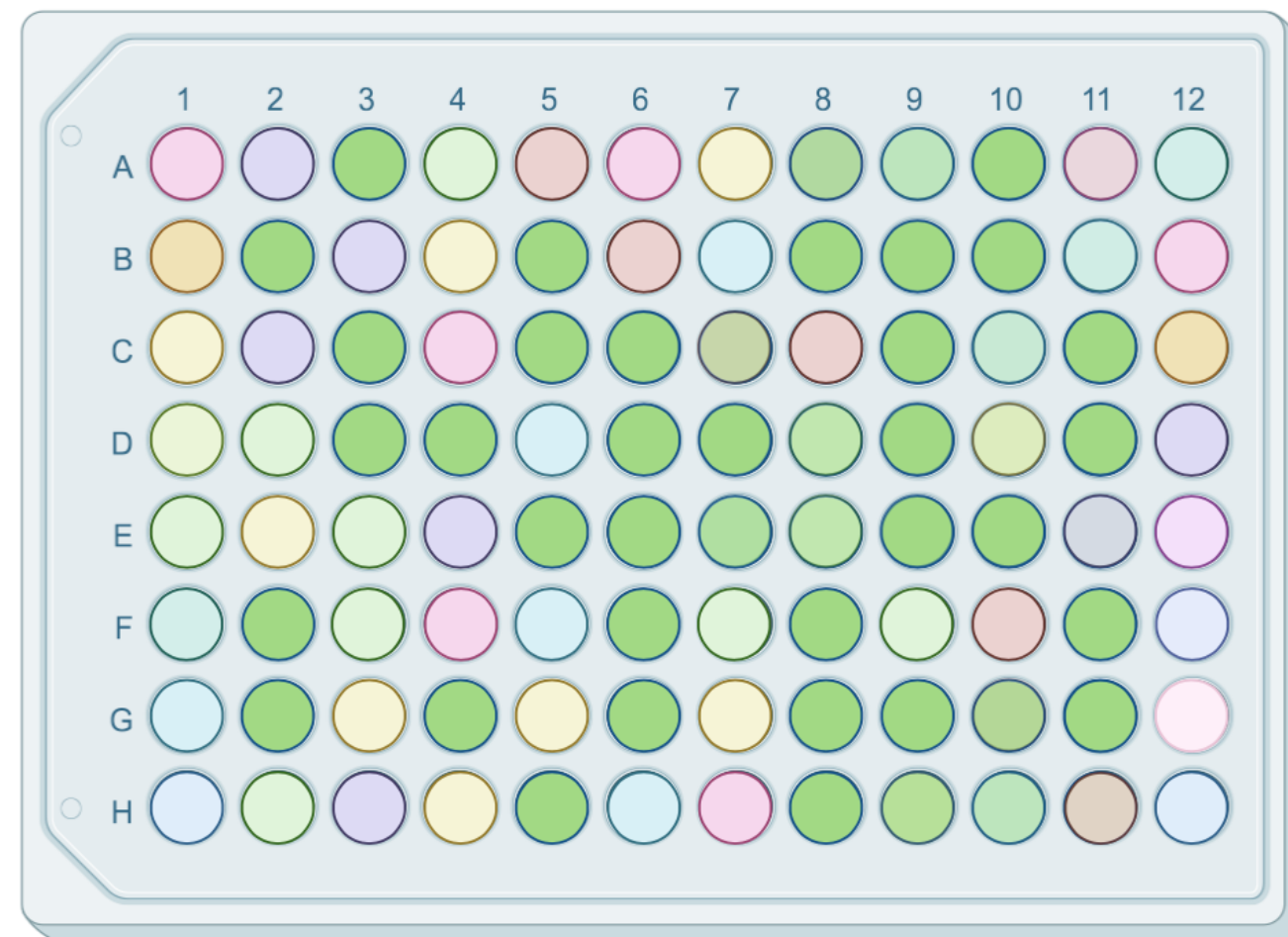
Fosmanogepix – Amplyx-Pfizer-Basilea

Fosmanogepix – Amplyx-Pfizer-Basilea

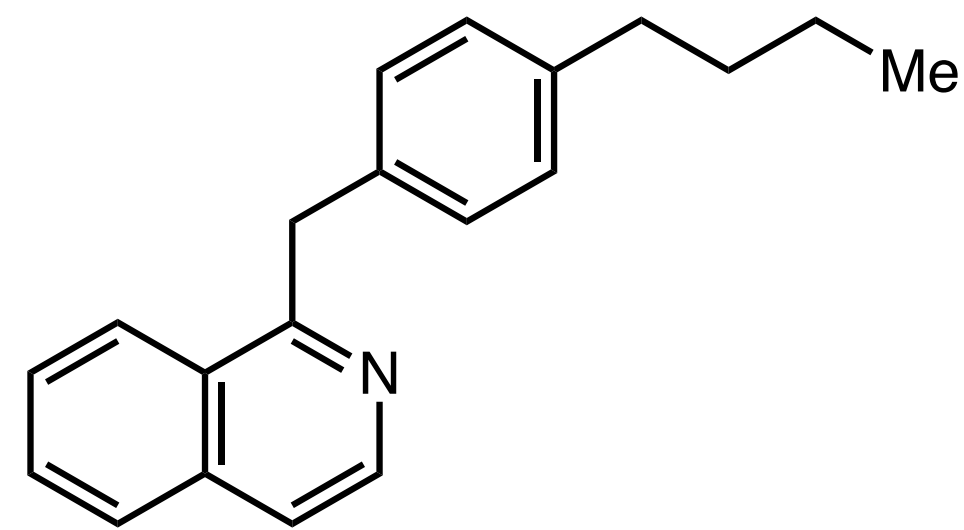


Desired Drug Compound – 2003
Interference with cell wall localization of mannoproteins

Fosmanogepix – Amplyx-Pfizer-Basilea



Compound screen

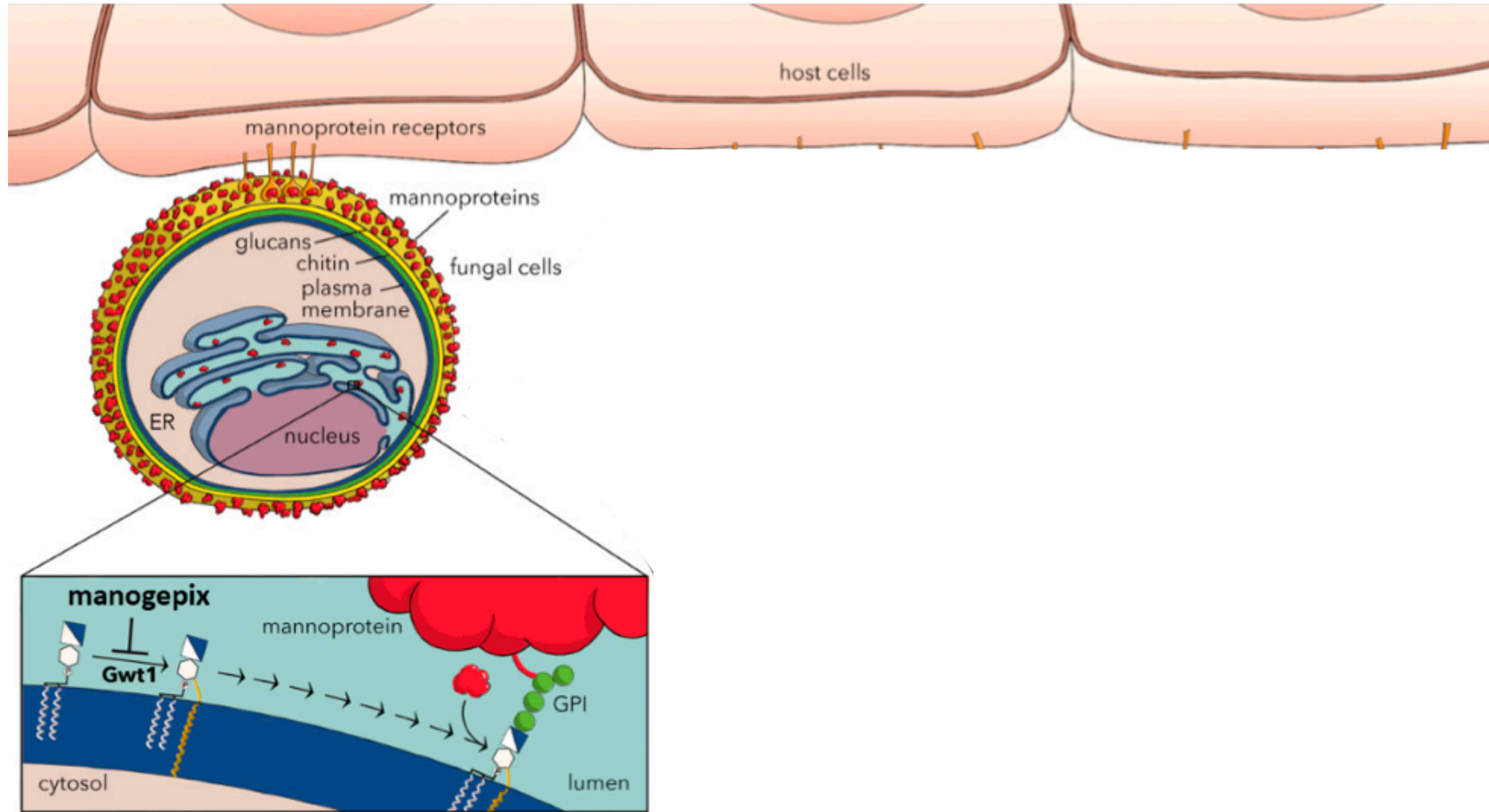


1-(4-butylbenzyl)isoquinoline (BIQ)
MIC: 1.56 $\mu\text{g}/\text{mL}$

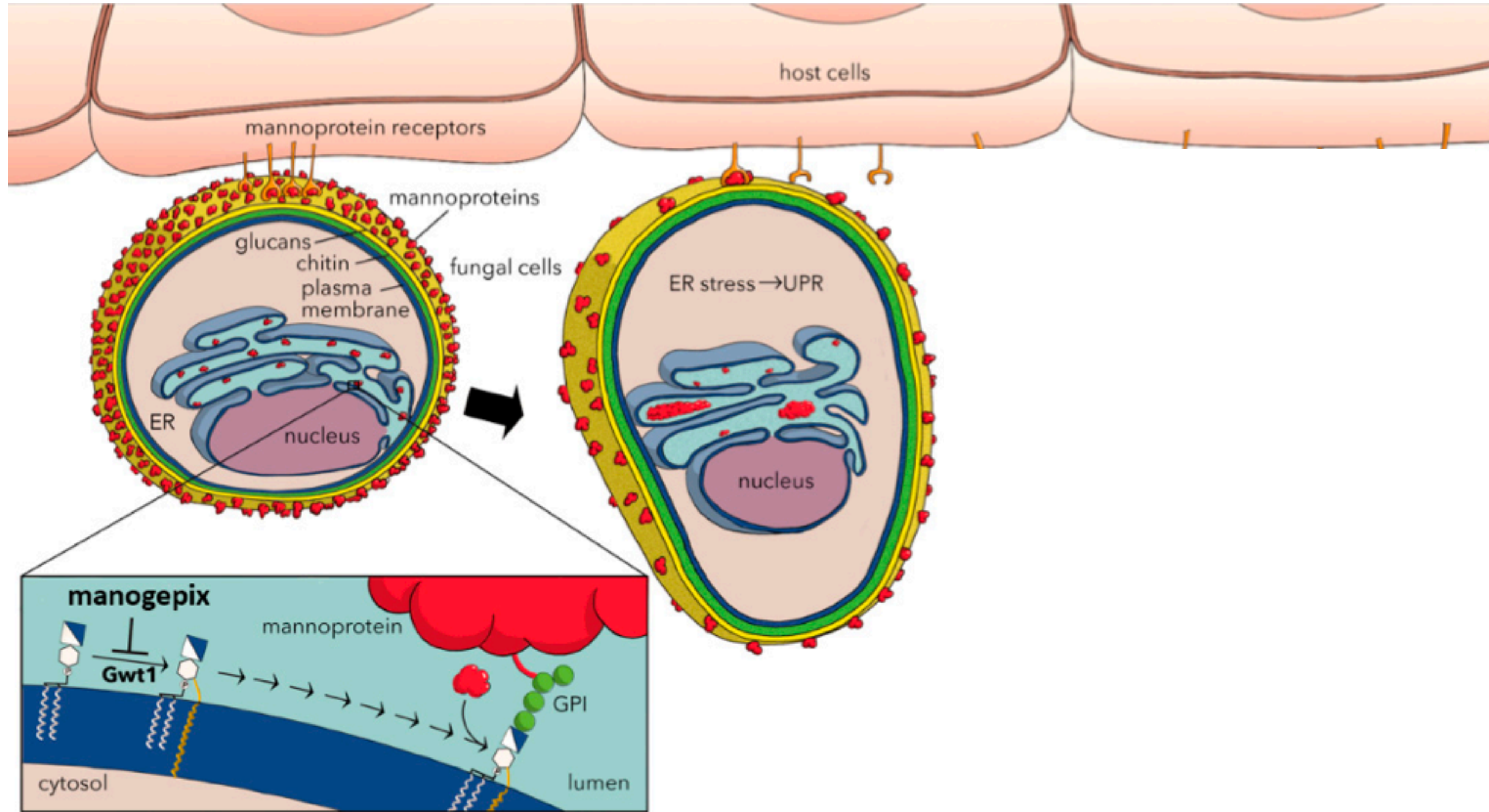


Genetic screening
Gwt1 enzyme

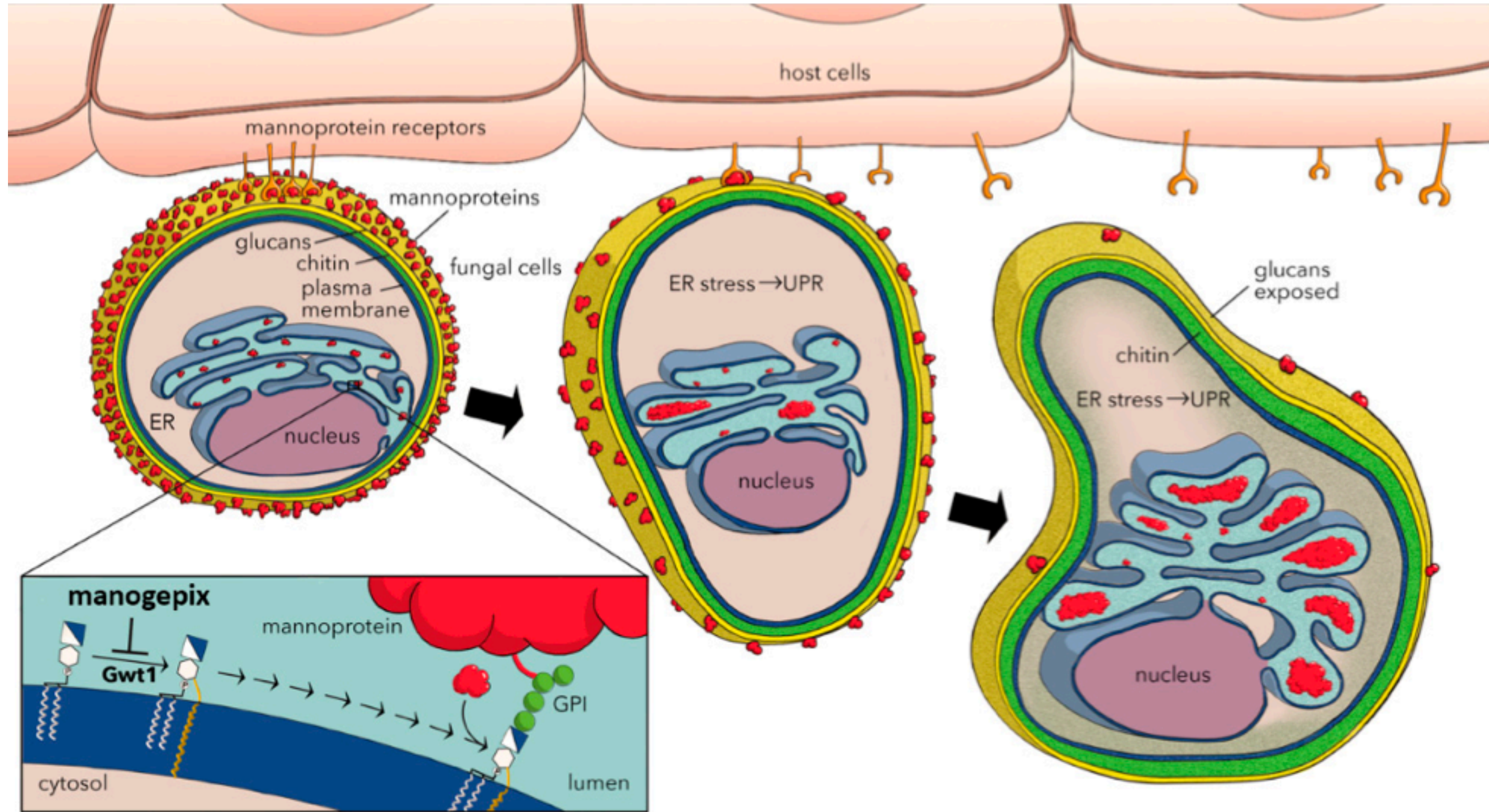
Fosmanogepix – Mechanism of Action



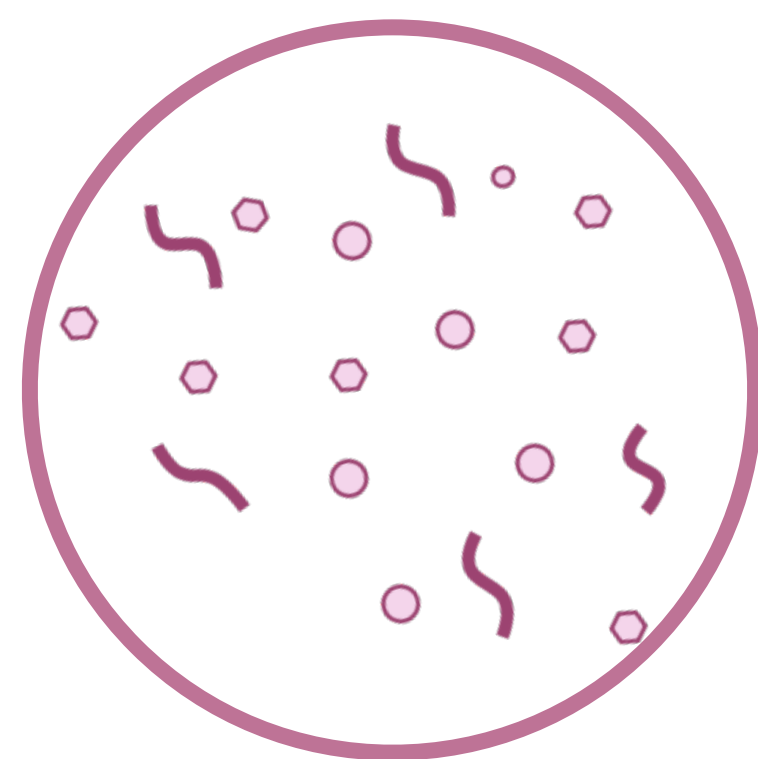
Fosmanogepix – Mechanism of Action



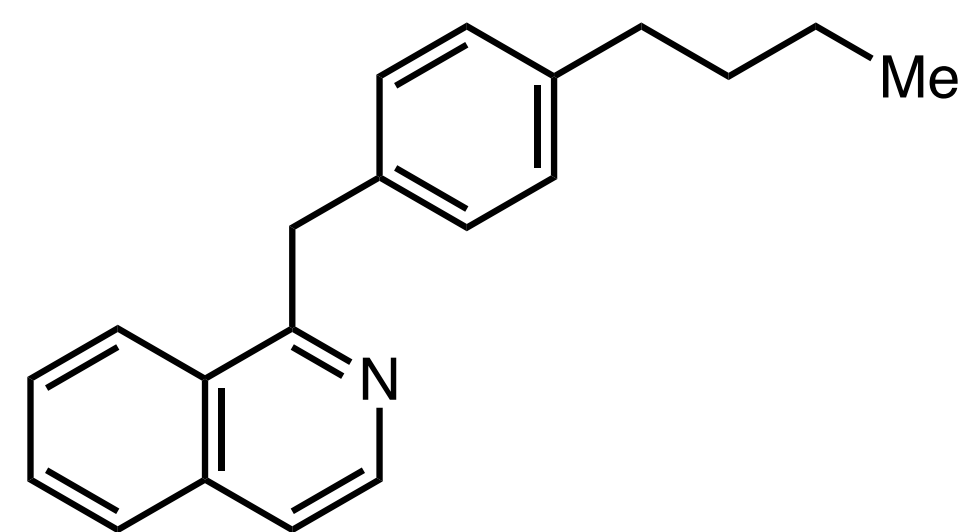
Fosmanogepix – Mechanism of Action



Fosmanogepix – Compound Screening



metabolically unstable
easily degraded



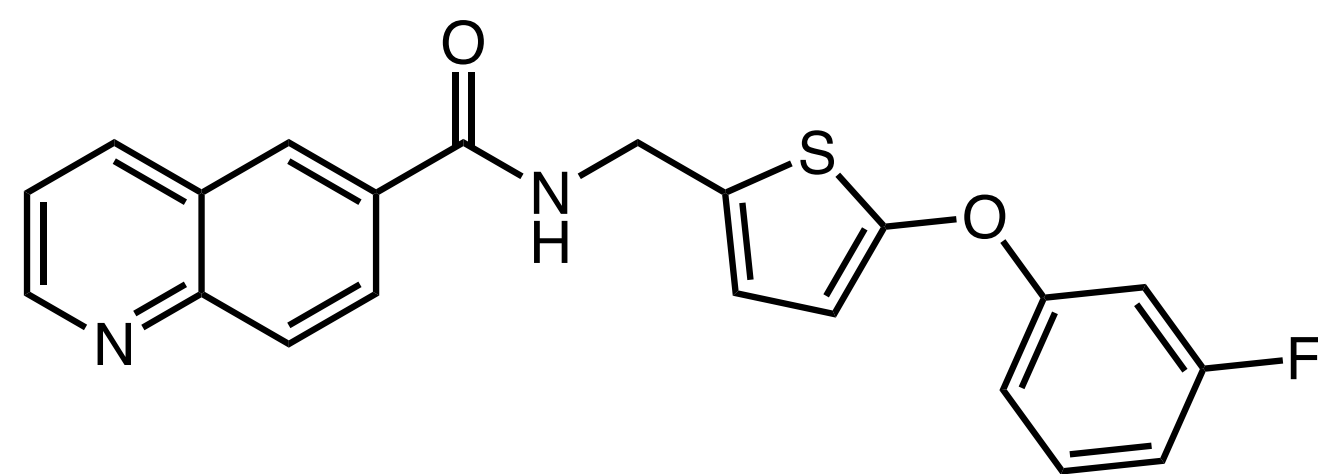
1-(4-butylbenzyl)isoquinoline (BIQ)



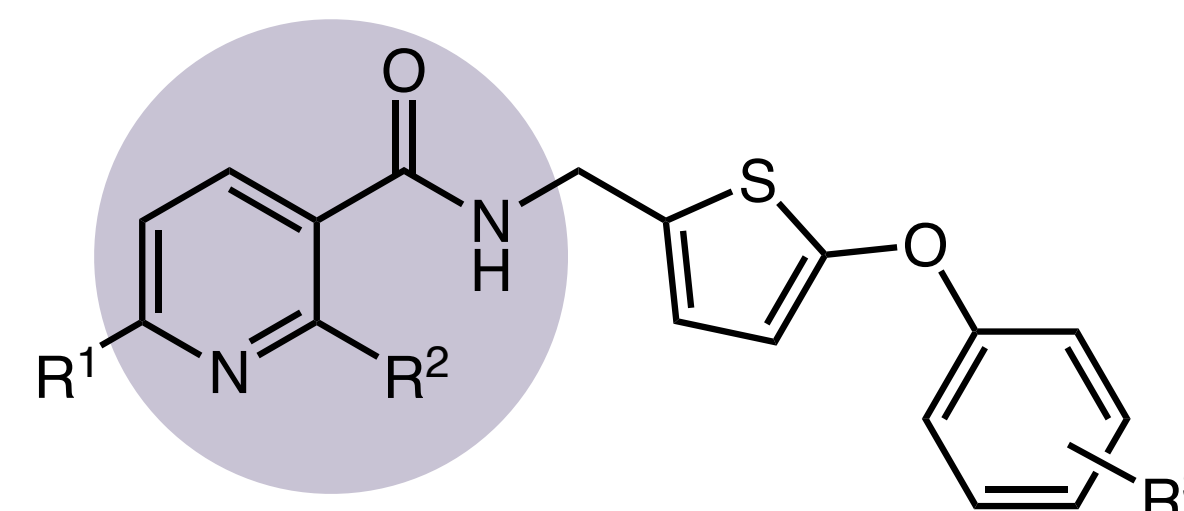
Aspergillosis
unaffected by BIQ

Fosmanogepix – Compound Screening

Fosmanogepix – Compound Screening



1

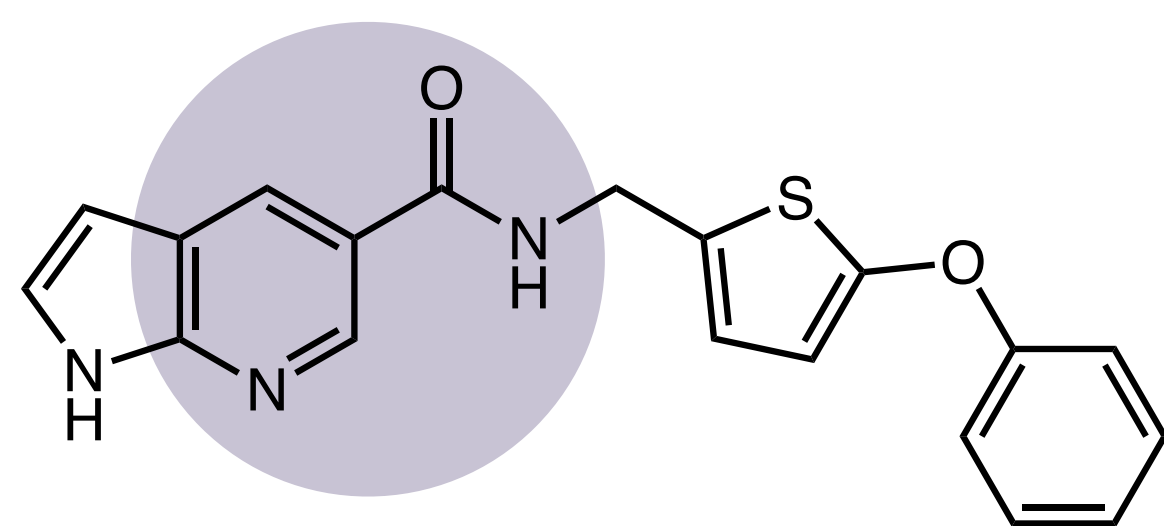


3A R1:NH₂; R2:H; R3: m-F

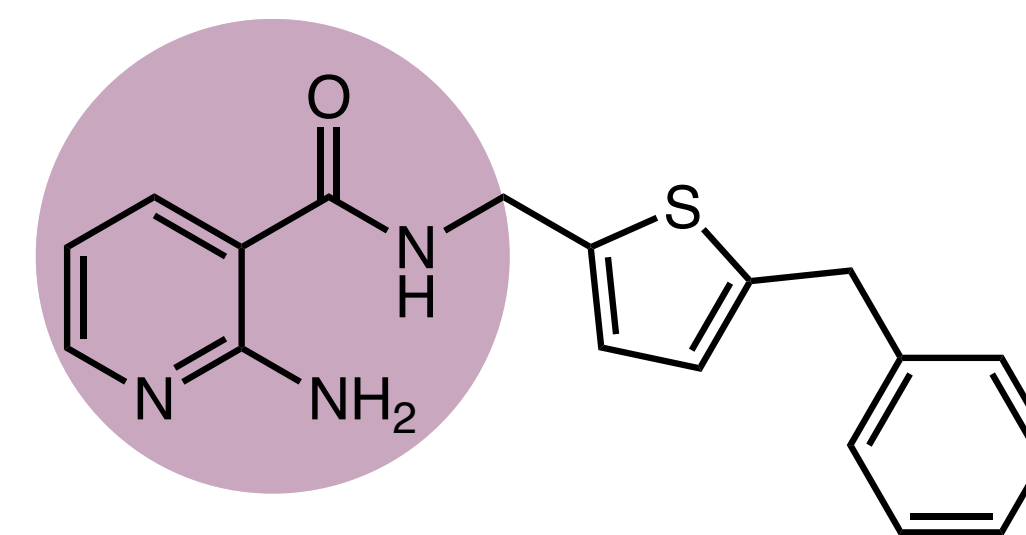
3B R1:H; R2:NH₂; R3: m-F

3C R1/R2:NH₂; R3:H

3D R1/R2:NH₂; R3:p-F

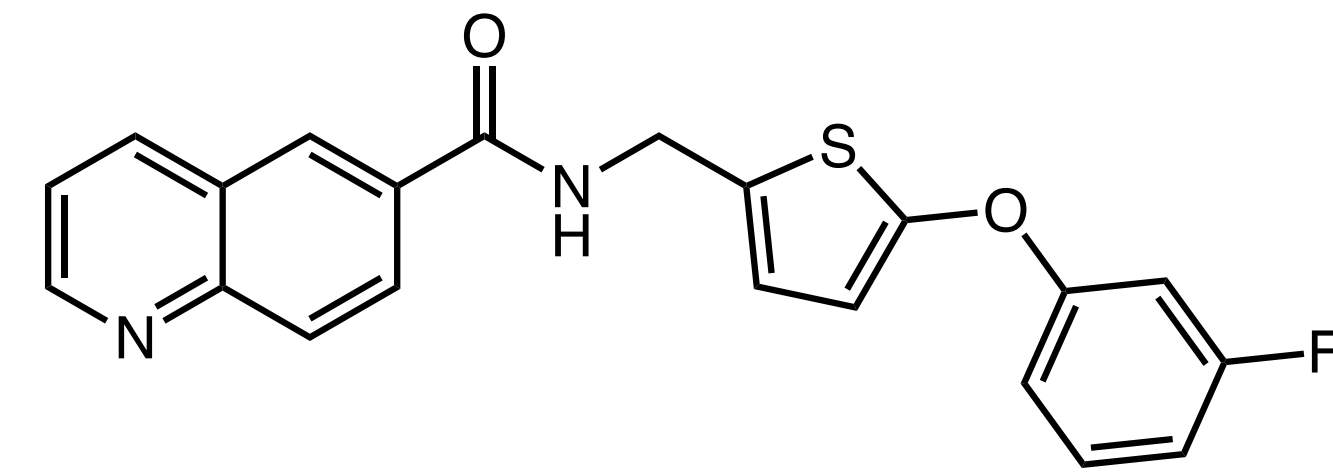


2

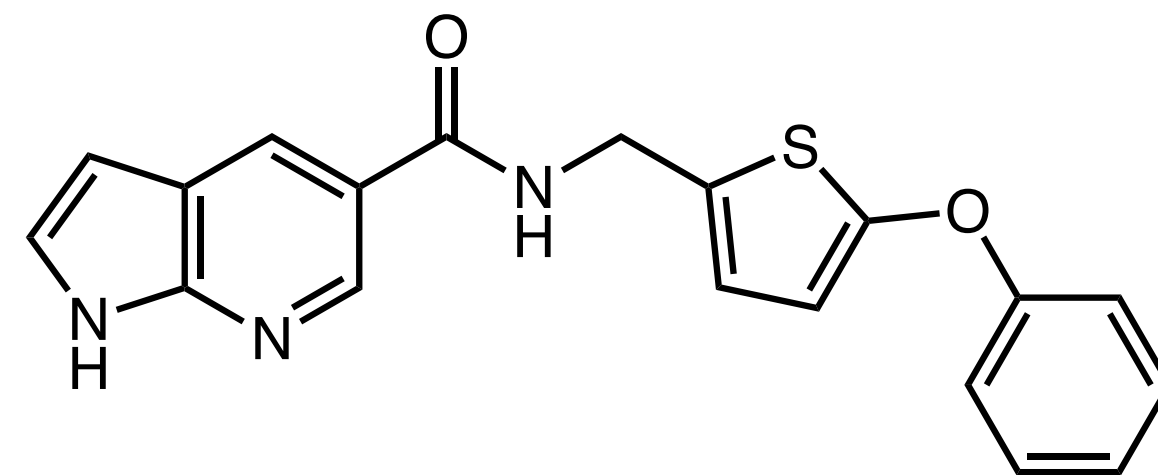


4

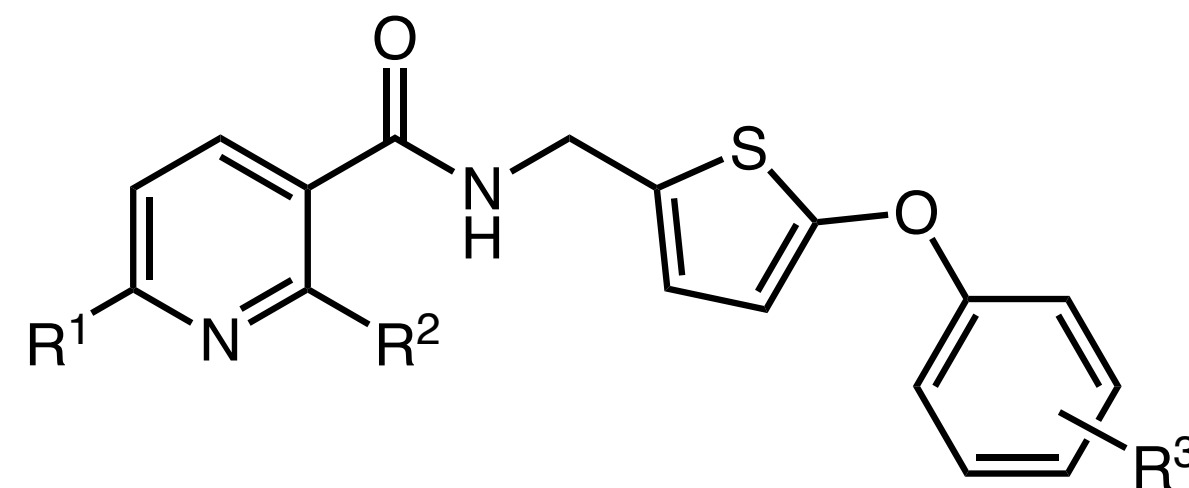
Fosmanogepix – Compound Screening



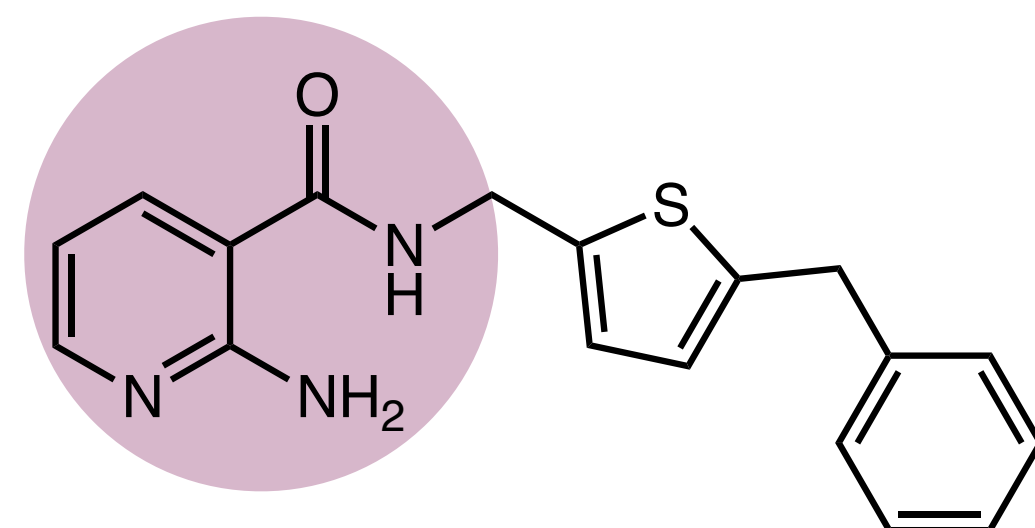
1



2



3A R1:NH₂; R2:H; R3: m-F
3B R1:H; R2:NH₂; R3: m-F
3C R1/R2:NH₂; R3:H
3D R1/R2:NH₂; R3:p-F

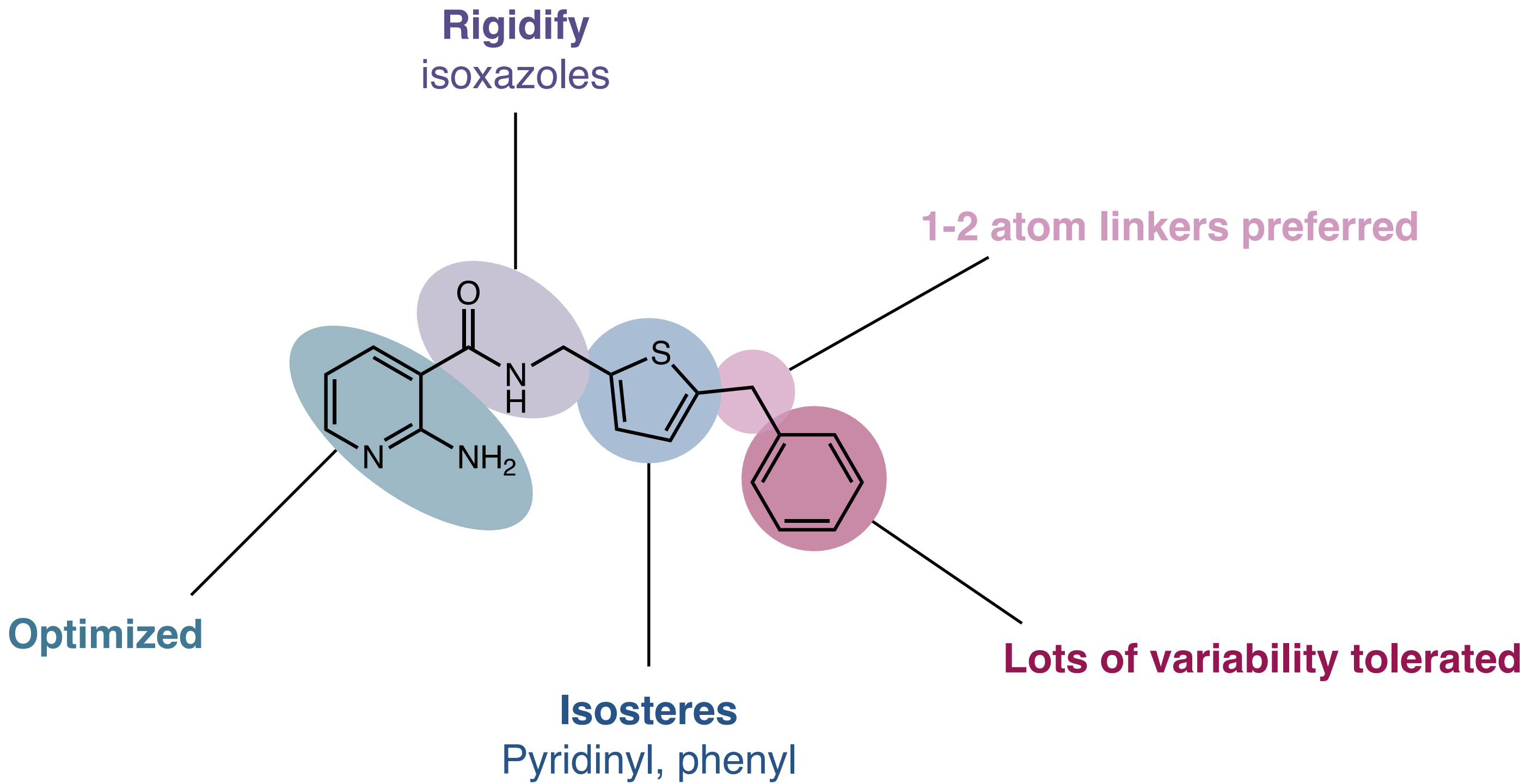


4

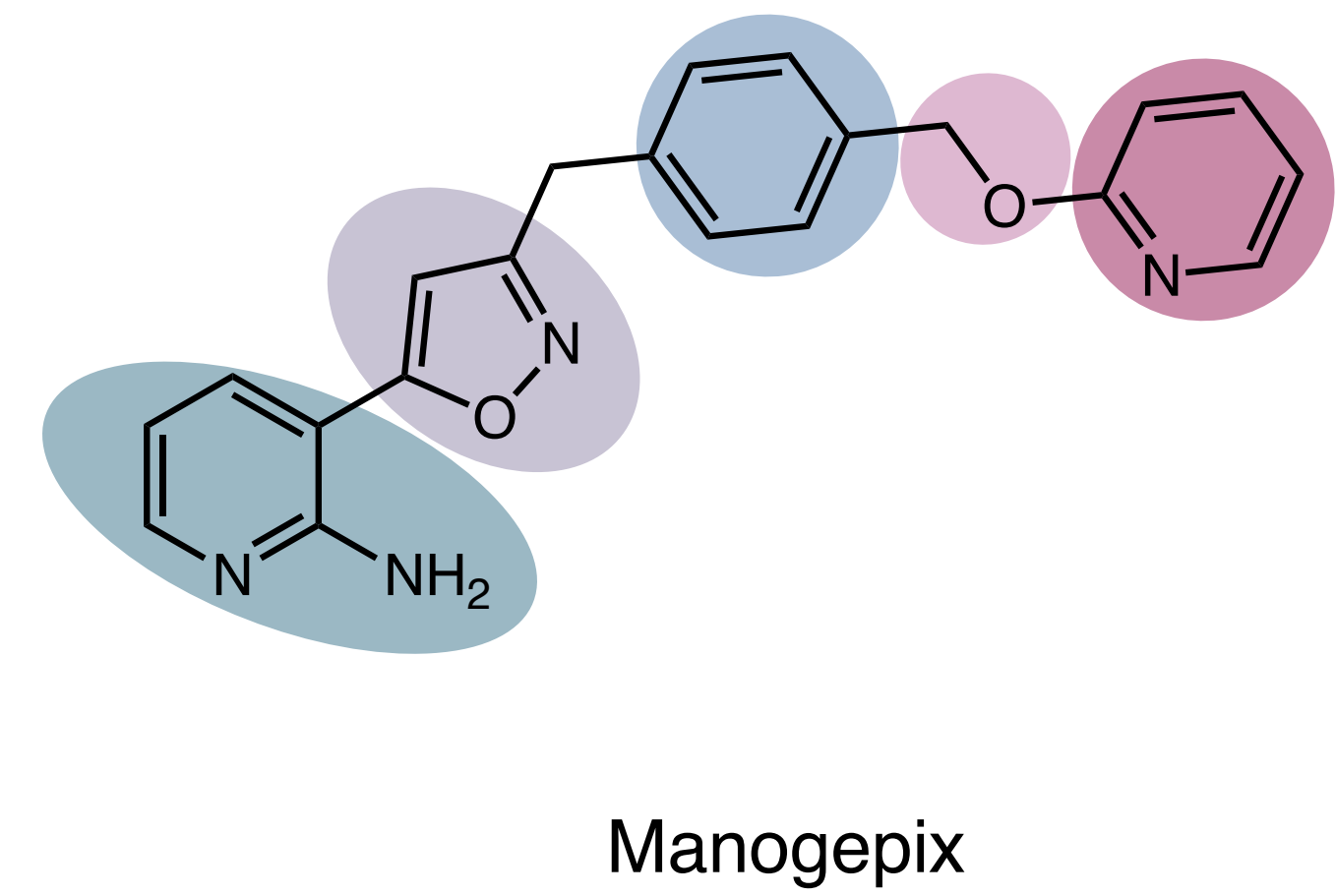
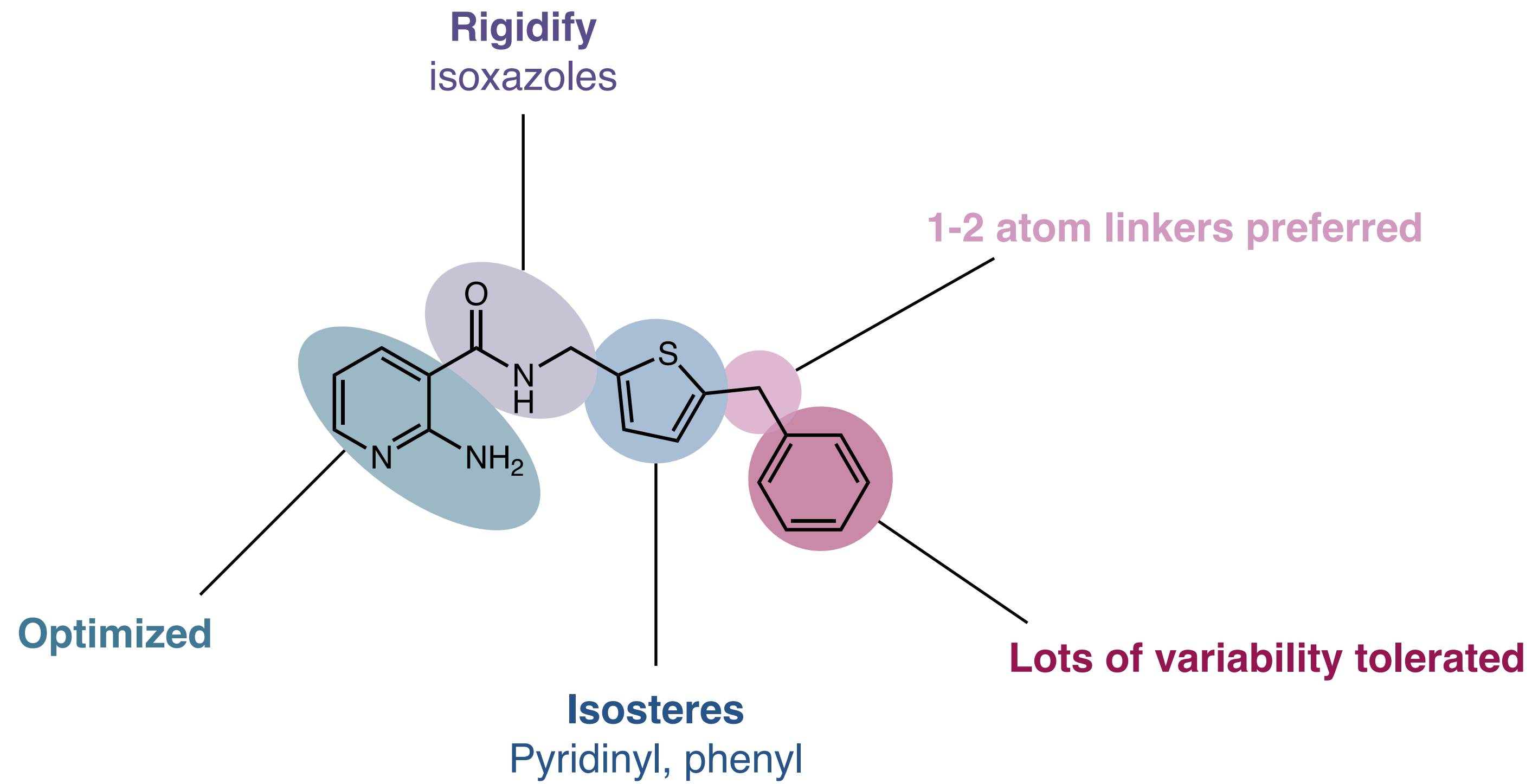
MIC (μg/mL)

Compound	<i>C. albicans</i>	<i>A. fumigatus</i>
1	0.1	1.56
2	0.39	3.13
3A	1.56	N.T.
3B	0.05	0.78
3C	0.78	1.56
3D	0.39	0.78
4	0.05	0.78
BIQ	1.56	N.T.
Fluconazole	0.39	N.T.
Amphotericin B	1.56	0.78

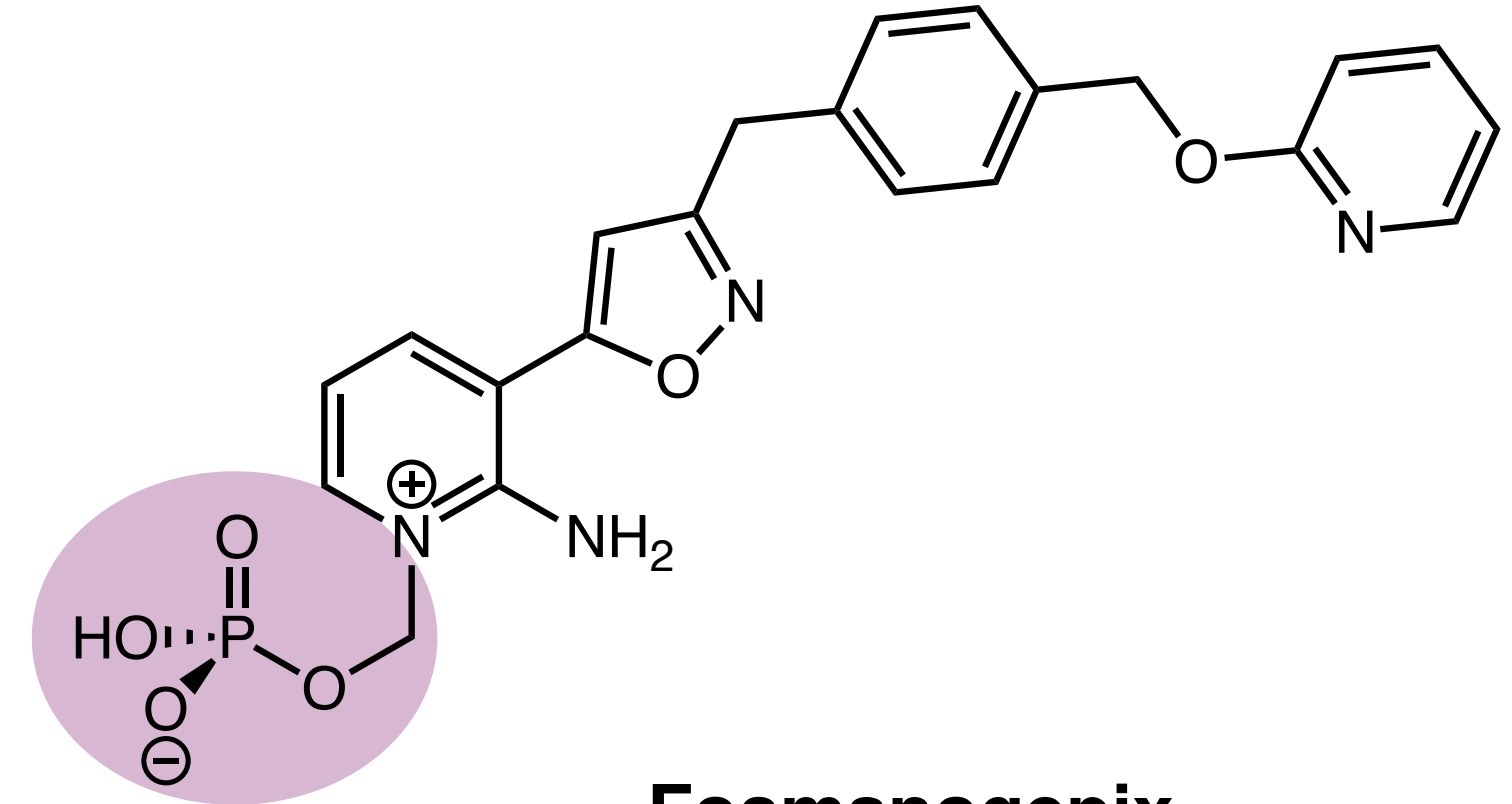
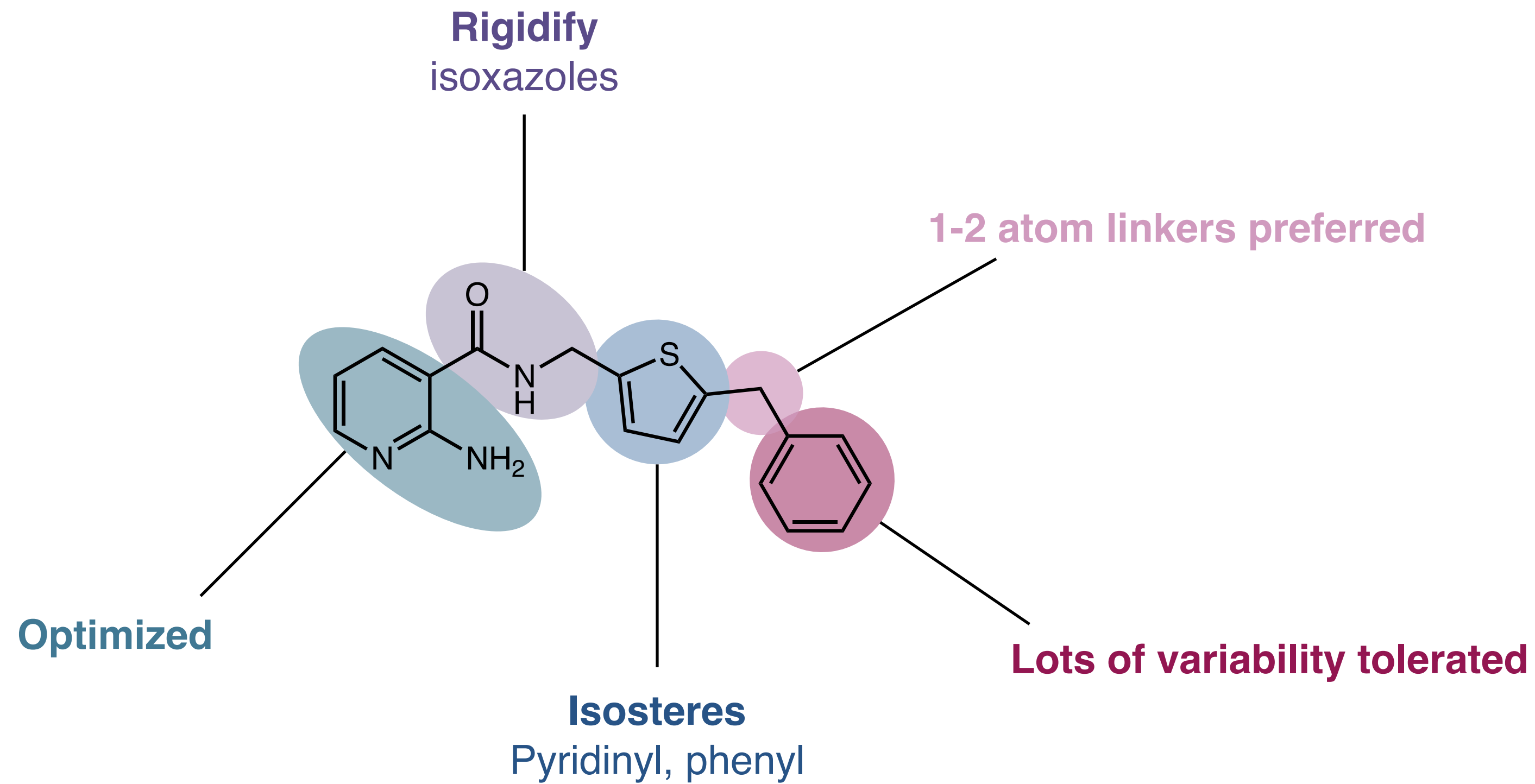
Fosmanogepix – Structure Activity Relationship



Fosmanogepix – Structure Activity Relationship



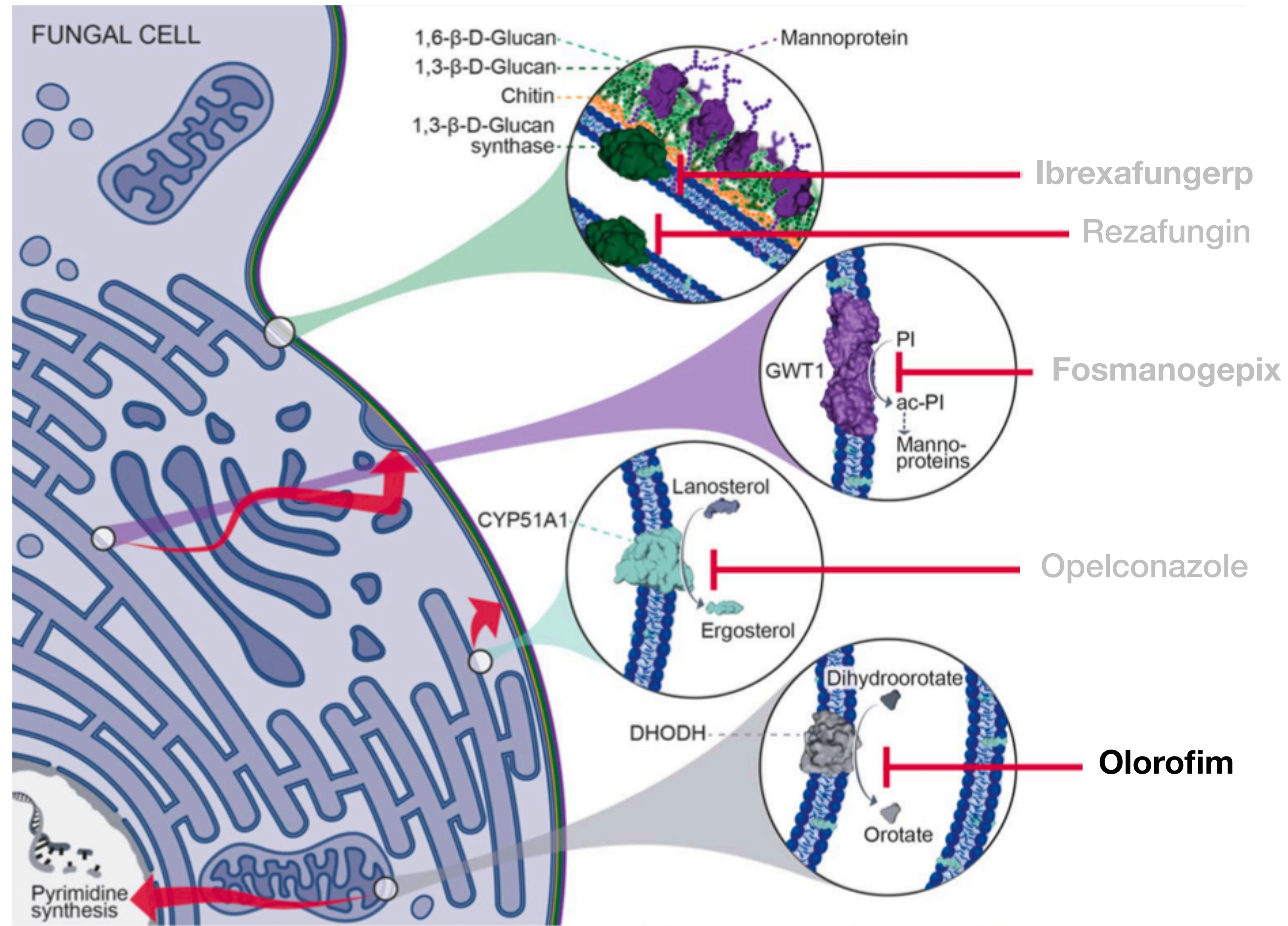
Fosmanogepix – Structure Activity Relationship



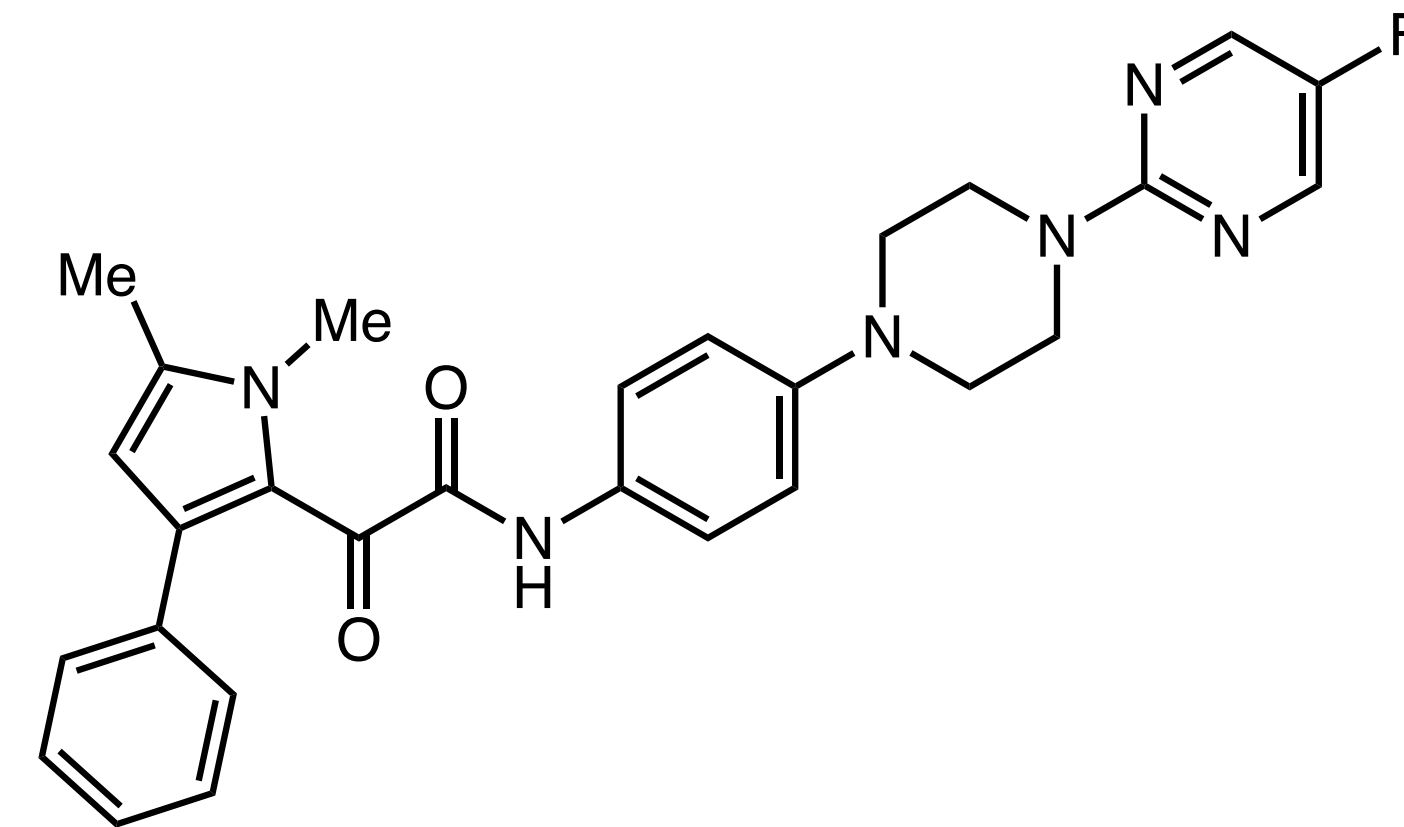
Fosmanogepix
improved aqueous solubility

good safety profile, in trials for invasive Candida infections.

Novel Drugs, Novel Mechanisms, Novel Delivery



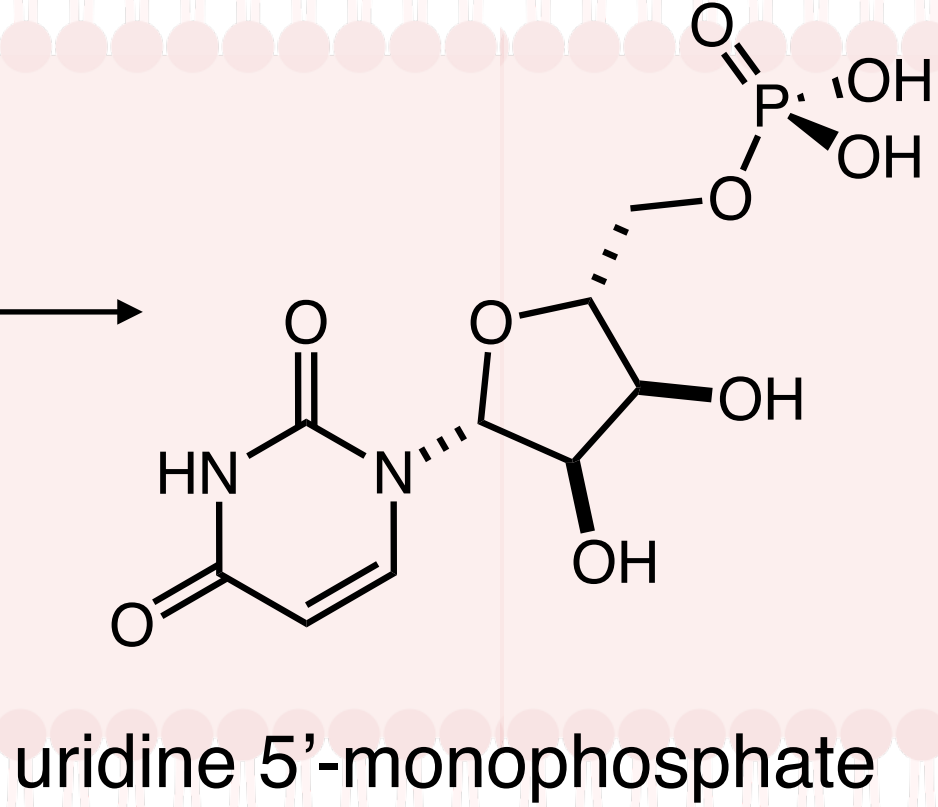
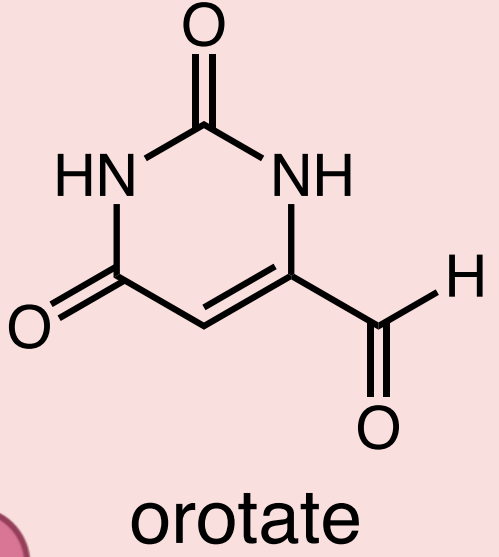
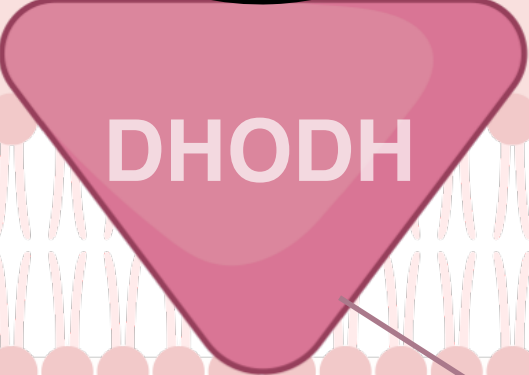
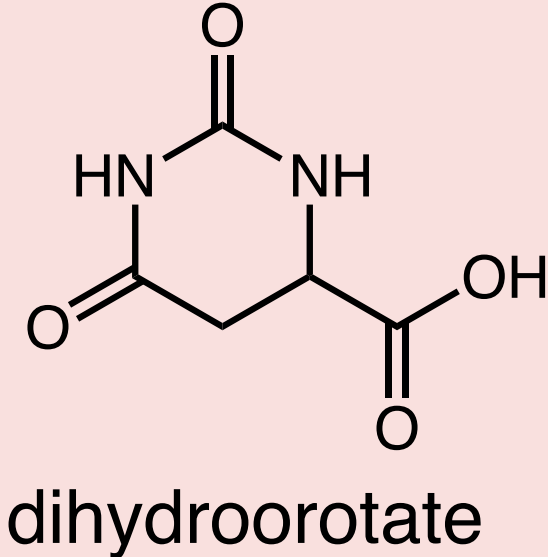
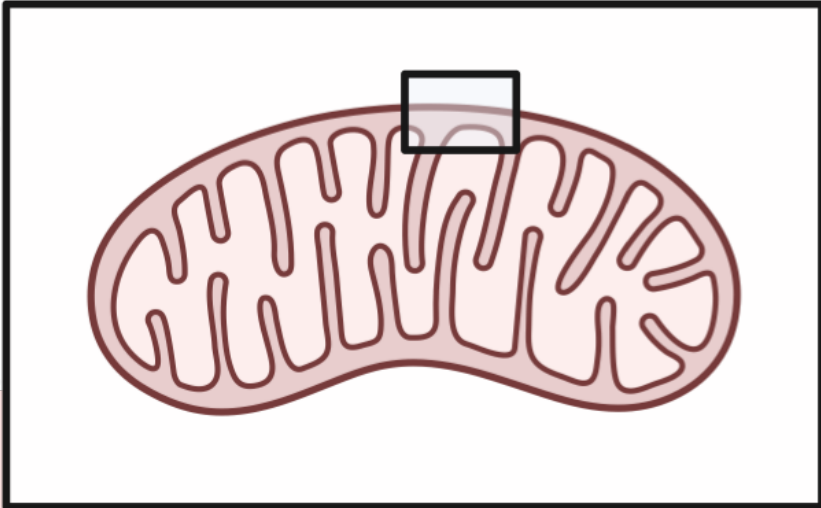
Olorofim – F2G



Orotomide – First in class
in clinical trials

Olorofim Mechanism of Action – F2G

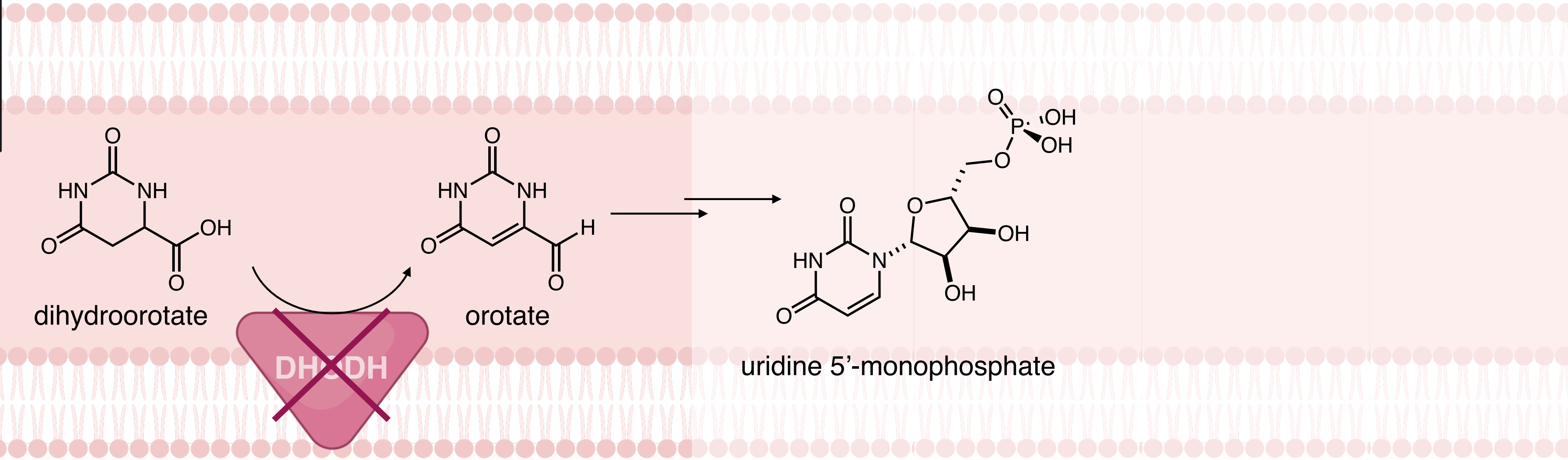
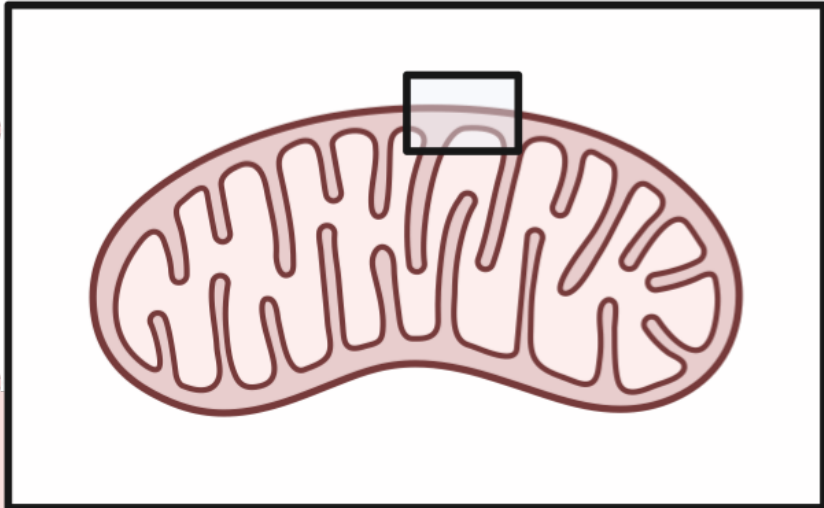
outer mitochondrial membrane



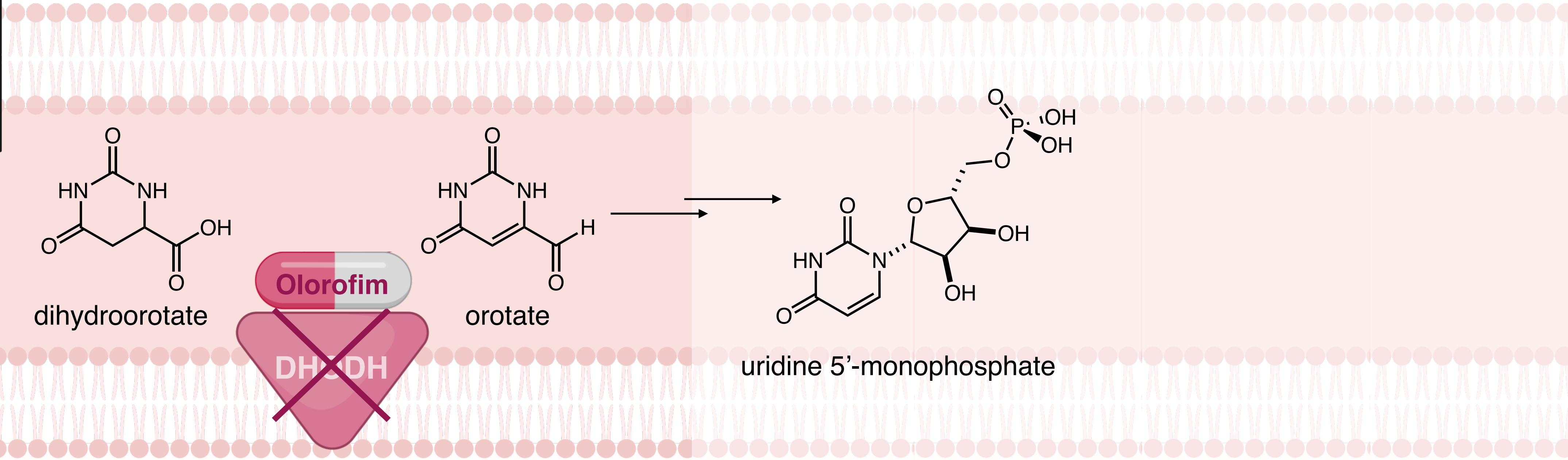
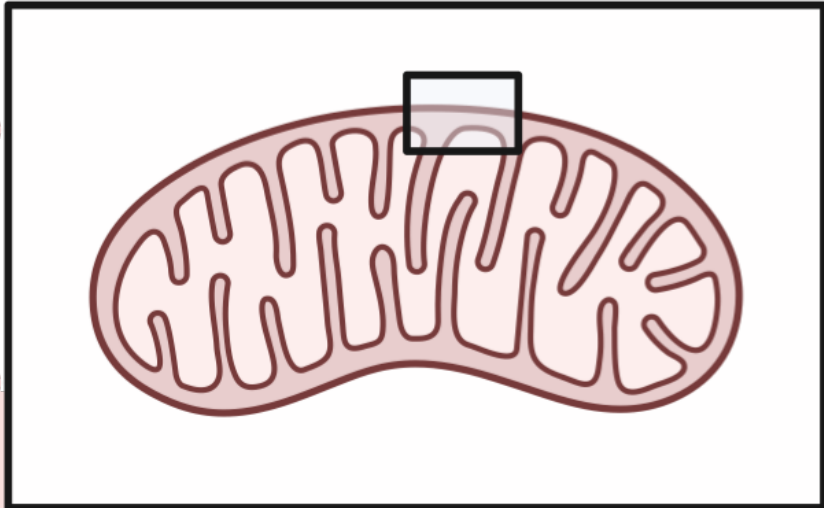
inner mitochondrial membrane

dihydroorotate dehydrogenase

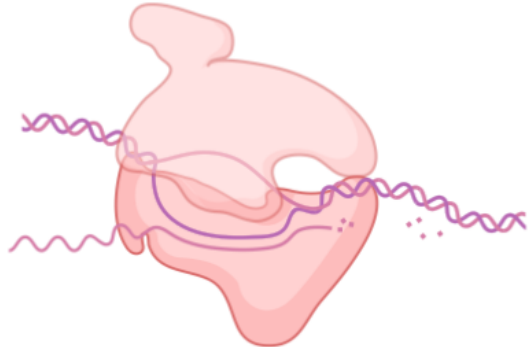
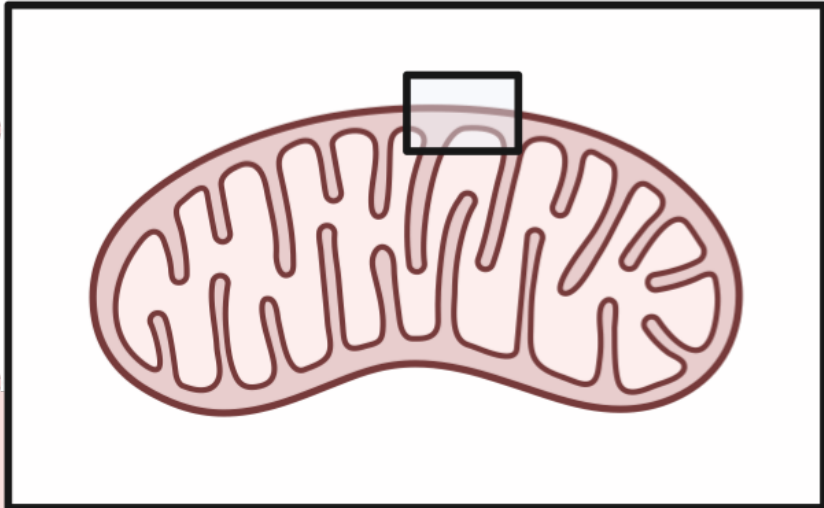
Olorofim Mechanism of Action – F2G



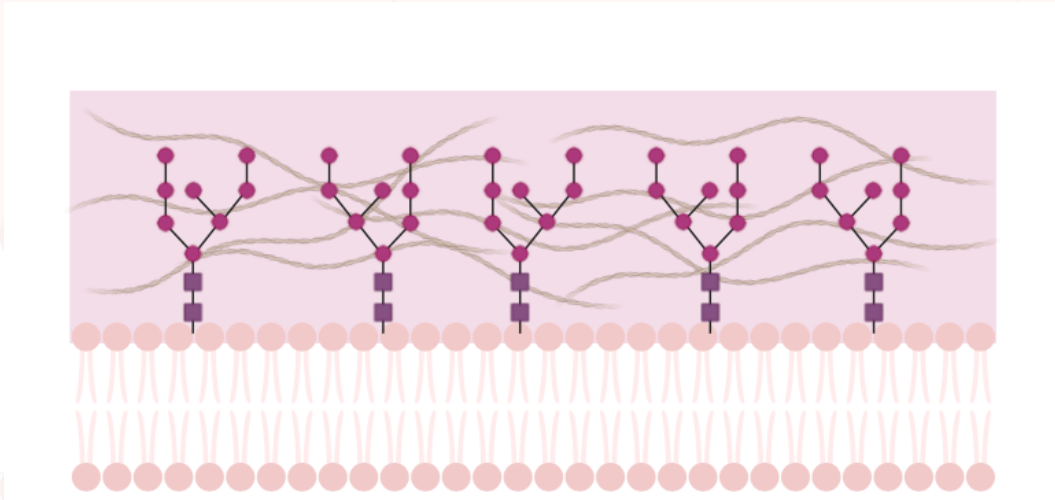
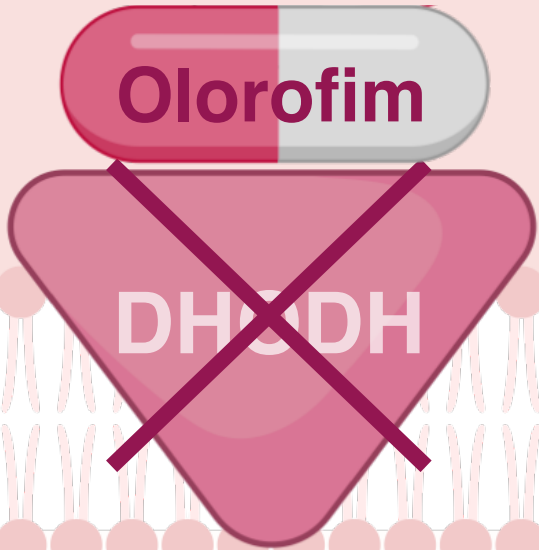
Olorofim Mechanism of Action – F2G



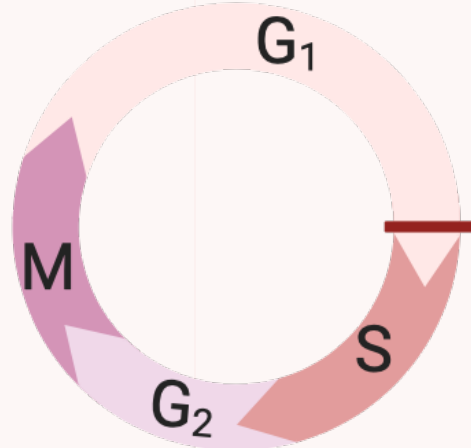
Olorofim Mechanism of Action – F2G



inhibition of nucleic acid synthesis
pyrimidines in RNA/DNA

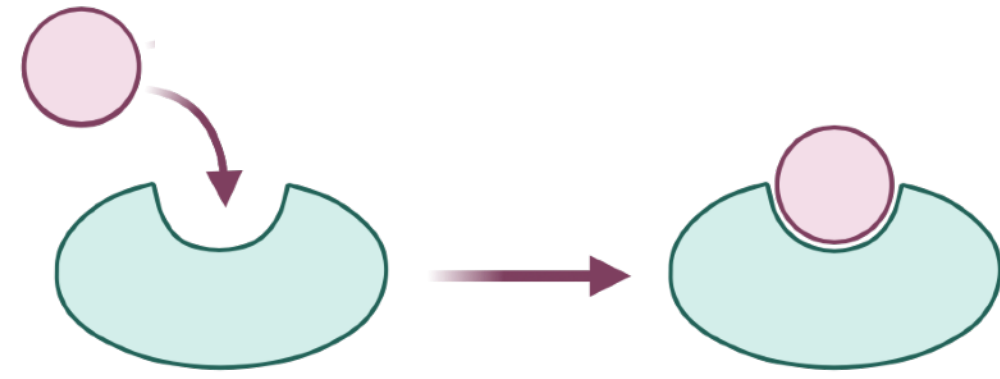


disruption of cell wall
glucan and chitin synthesis

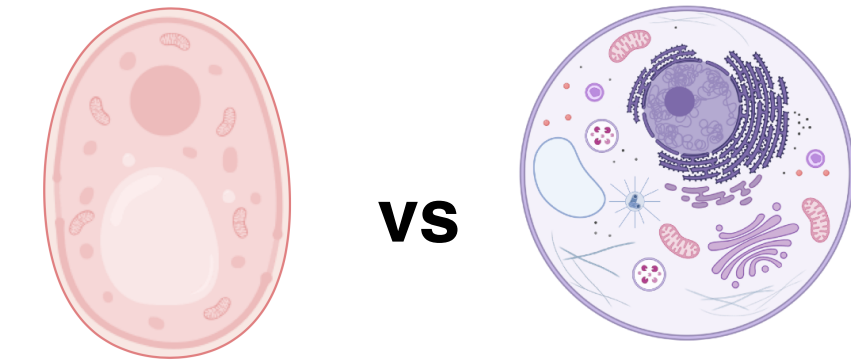


Cell cycle arrest

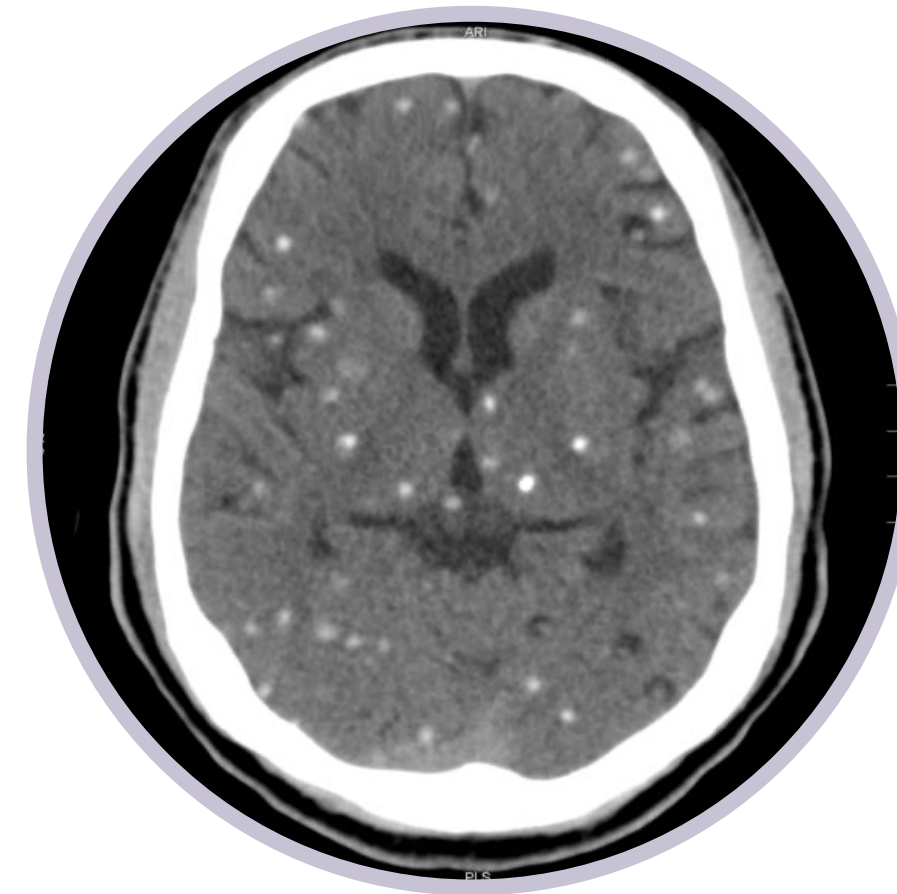
Olorofim – F2G



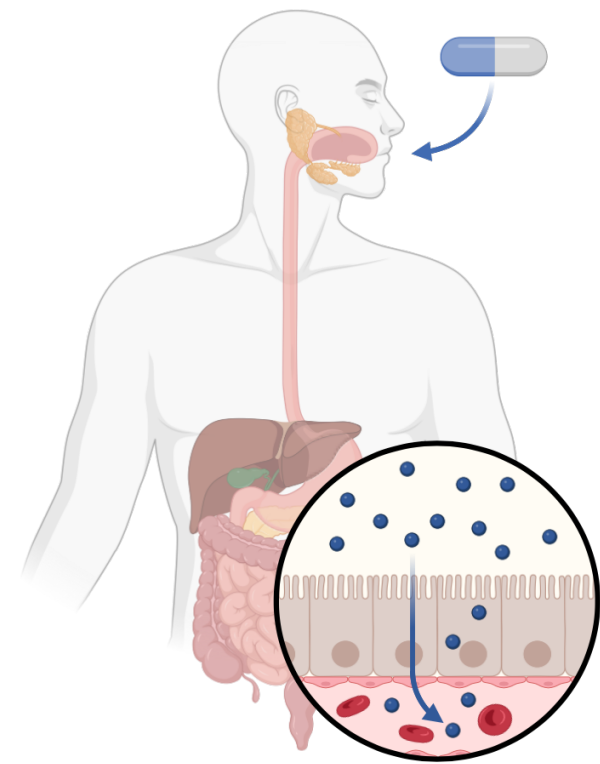
novel mechanism
activity against multi-resistant strains



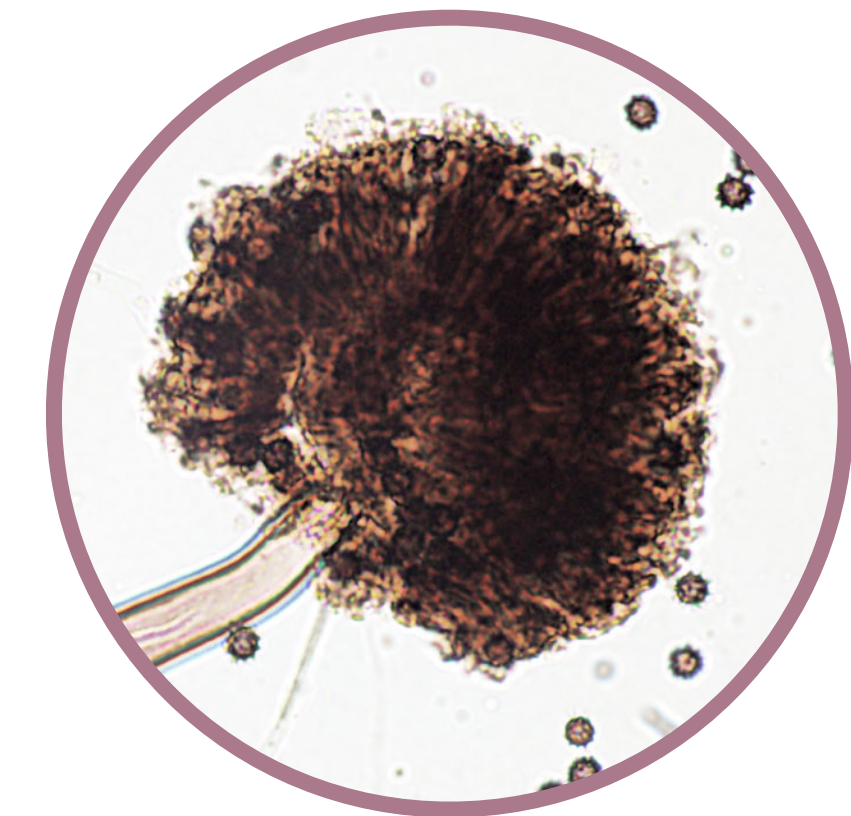
fungal specificity
minimal cross reactivity with human DHODH



CNS activity
potential *Coccidioidomycosis* treatment



good bioavailability
oral dosing, good tissue penetration



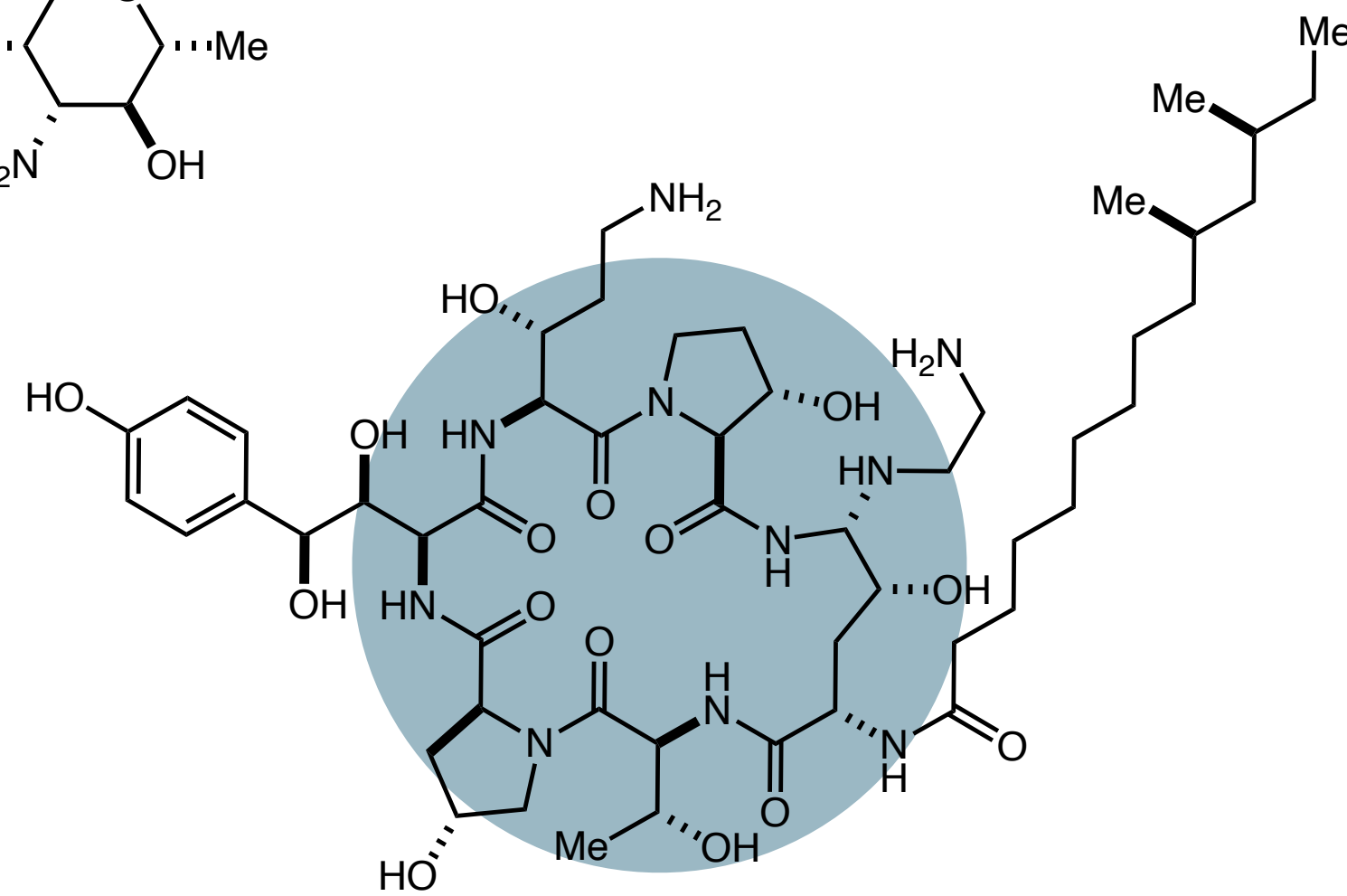
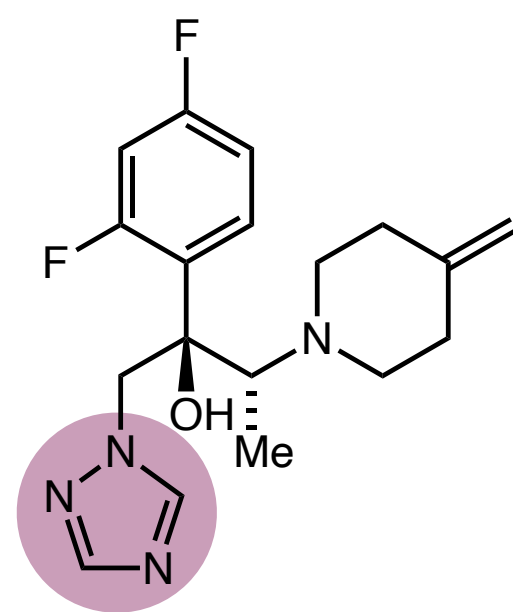
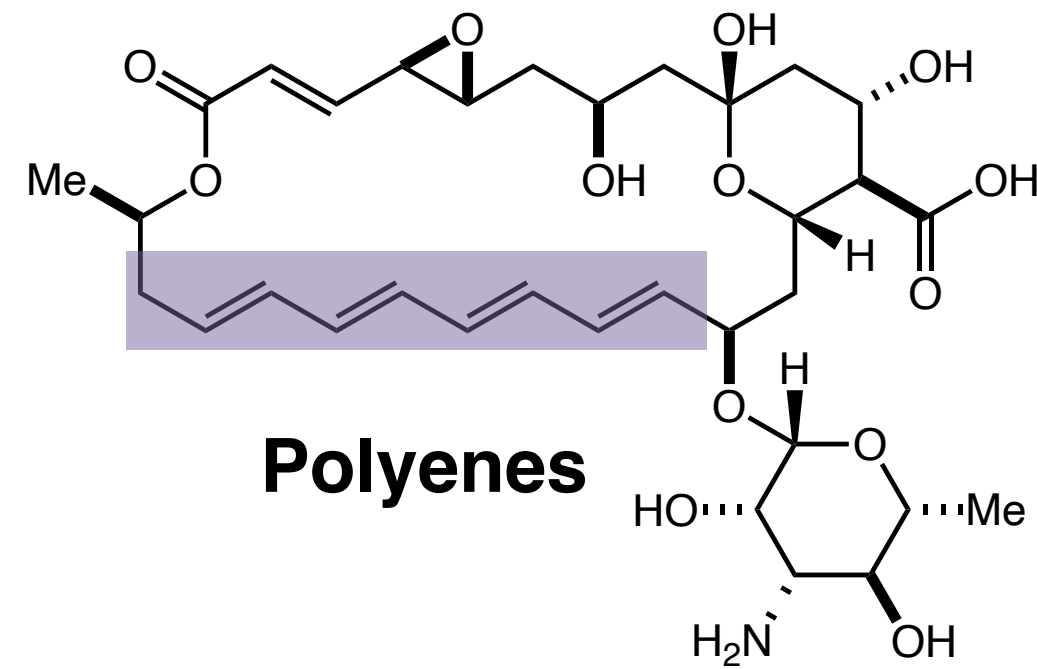
unique, complementary spectrum
activity against molds,
thermally dimorphic fungi

Oliver, J. D. et al. *PNAS*. 2016, 113(45), 12809–12814.

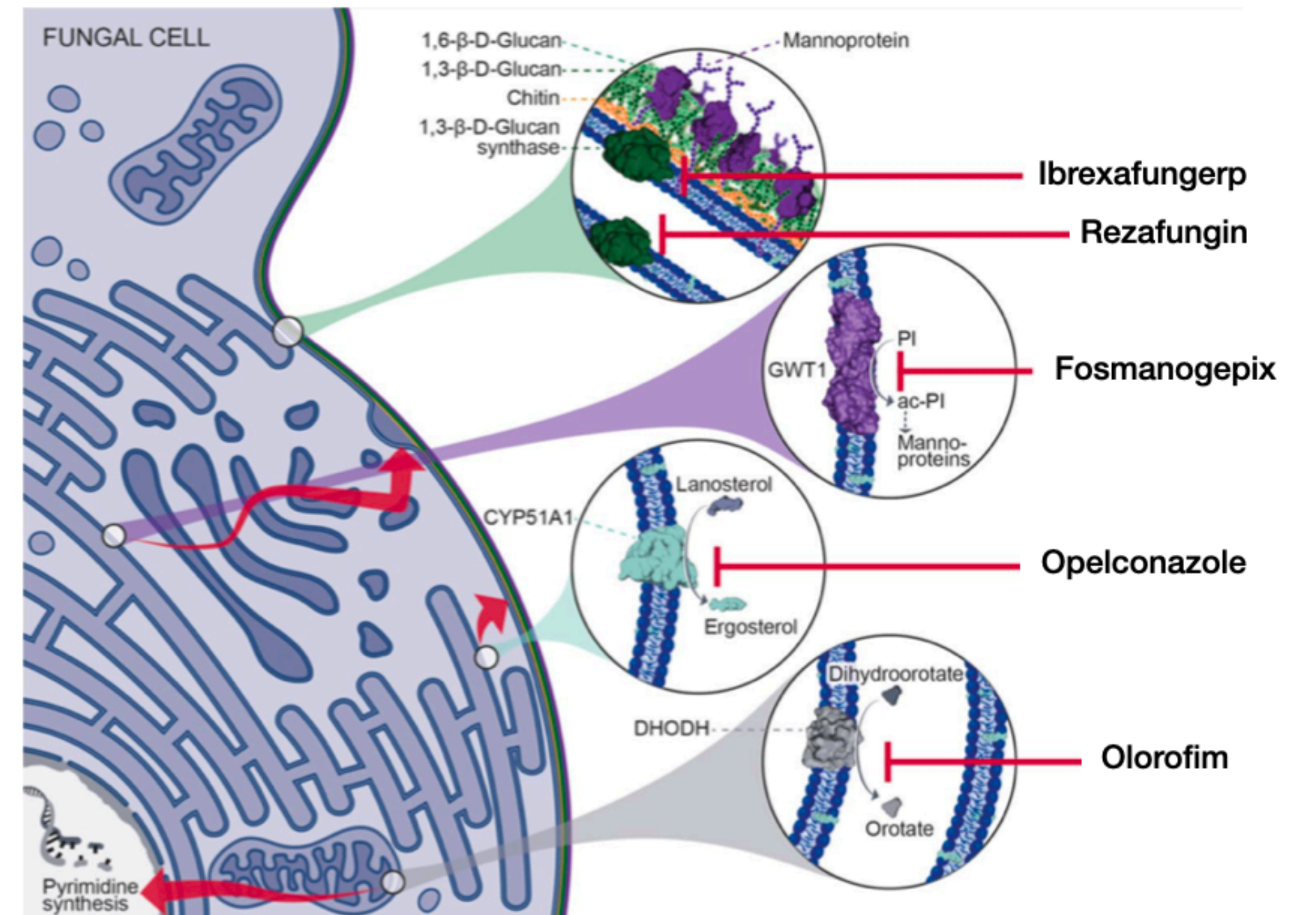
Wiederhold, N. P. *J. Fungi*. 2020, 6(3), 122.

At a Glance

The Past

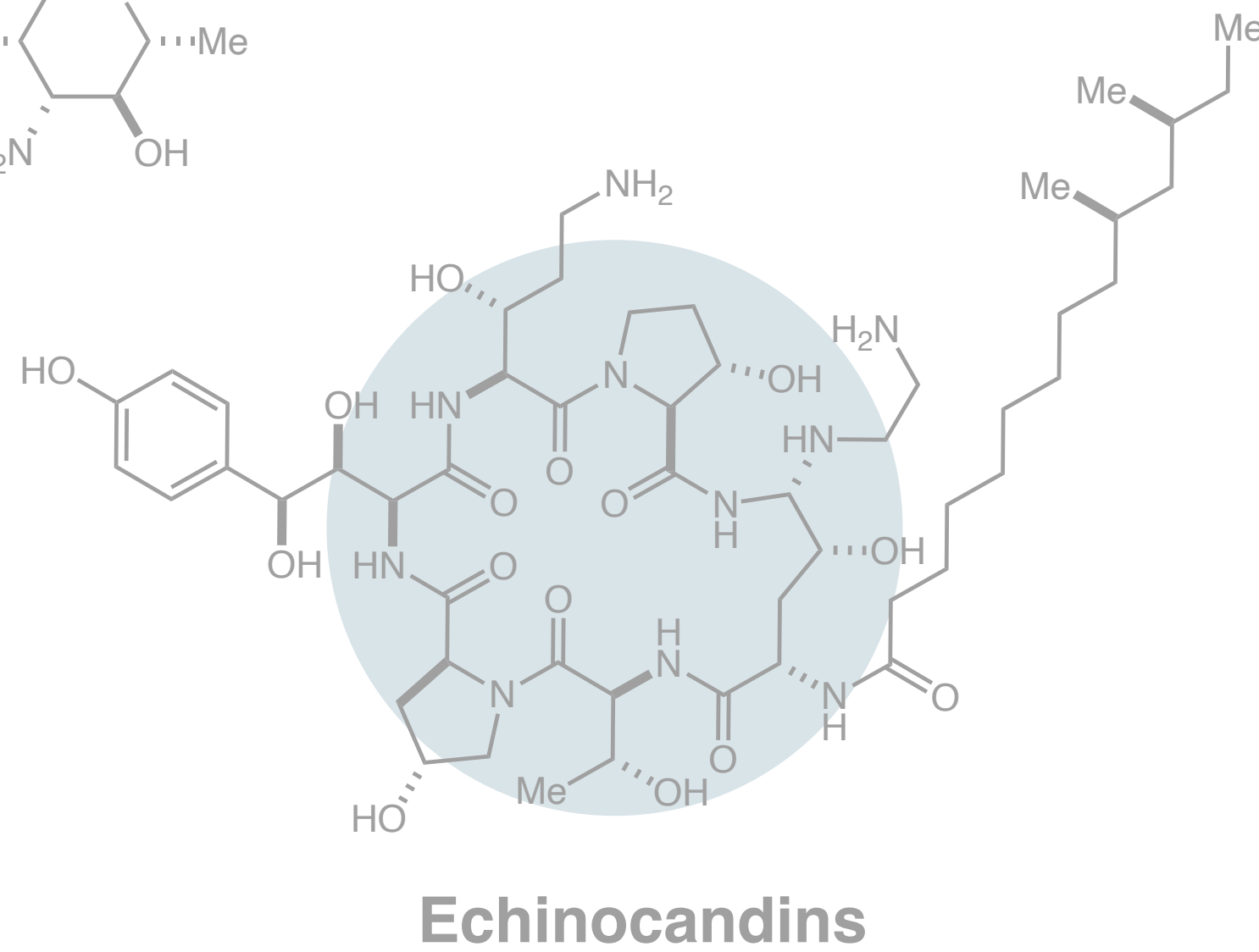
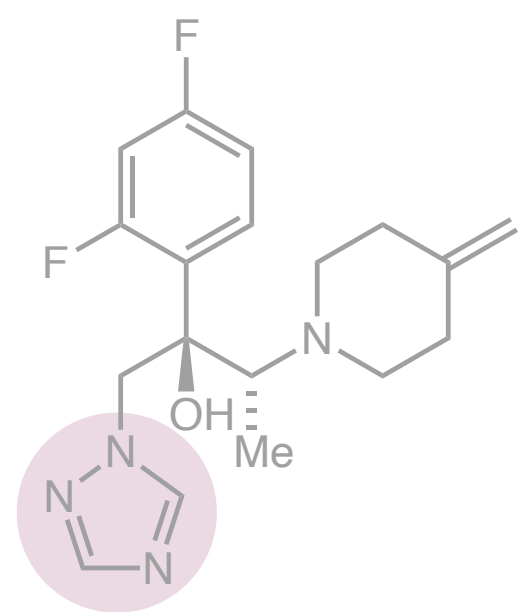
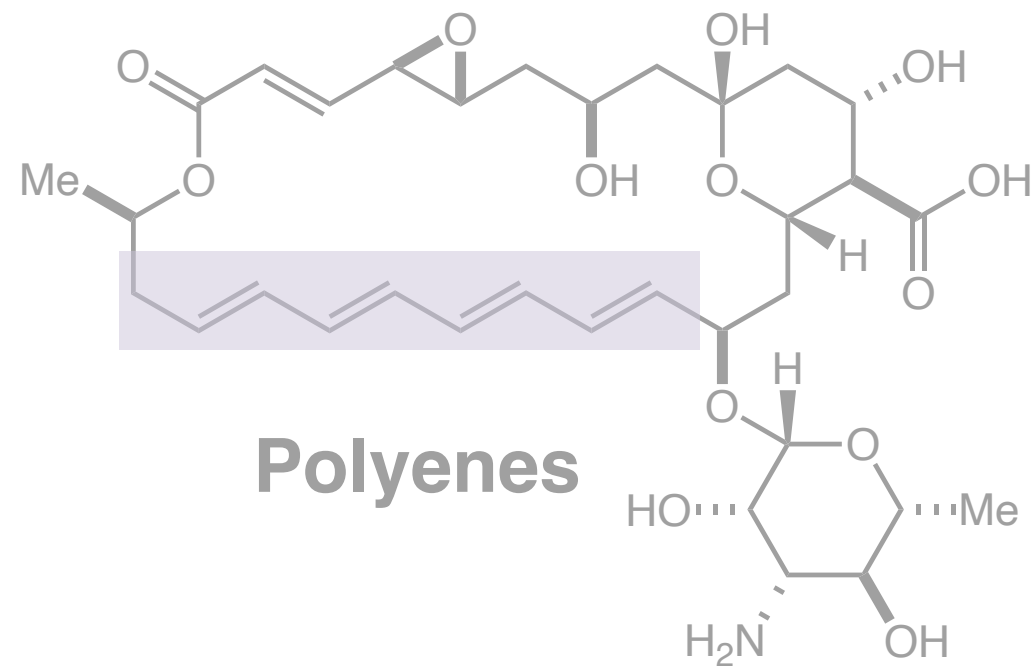


The Future



Questions?

The Past



The Future

