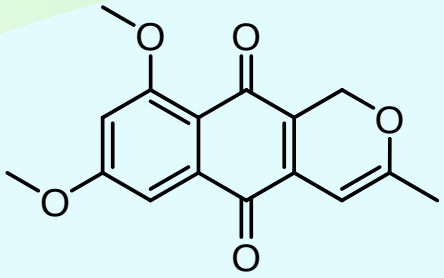
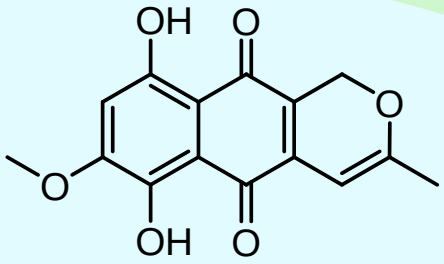
The Role of Universities in Research for Developing Natural Products as Medicines

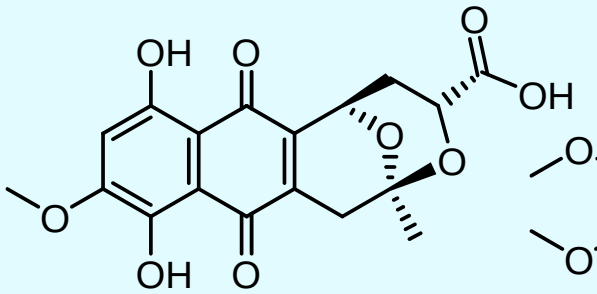
Charles de Koning



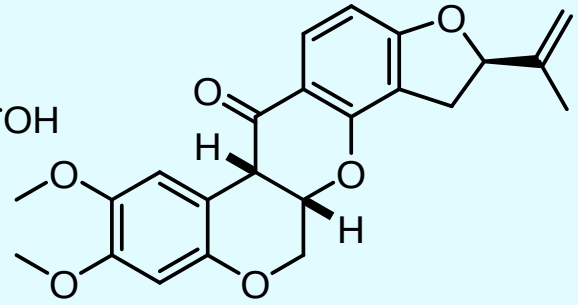
Dehydroherbarin



Anhydrofusarubin



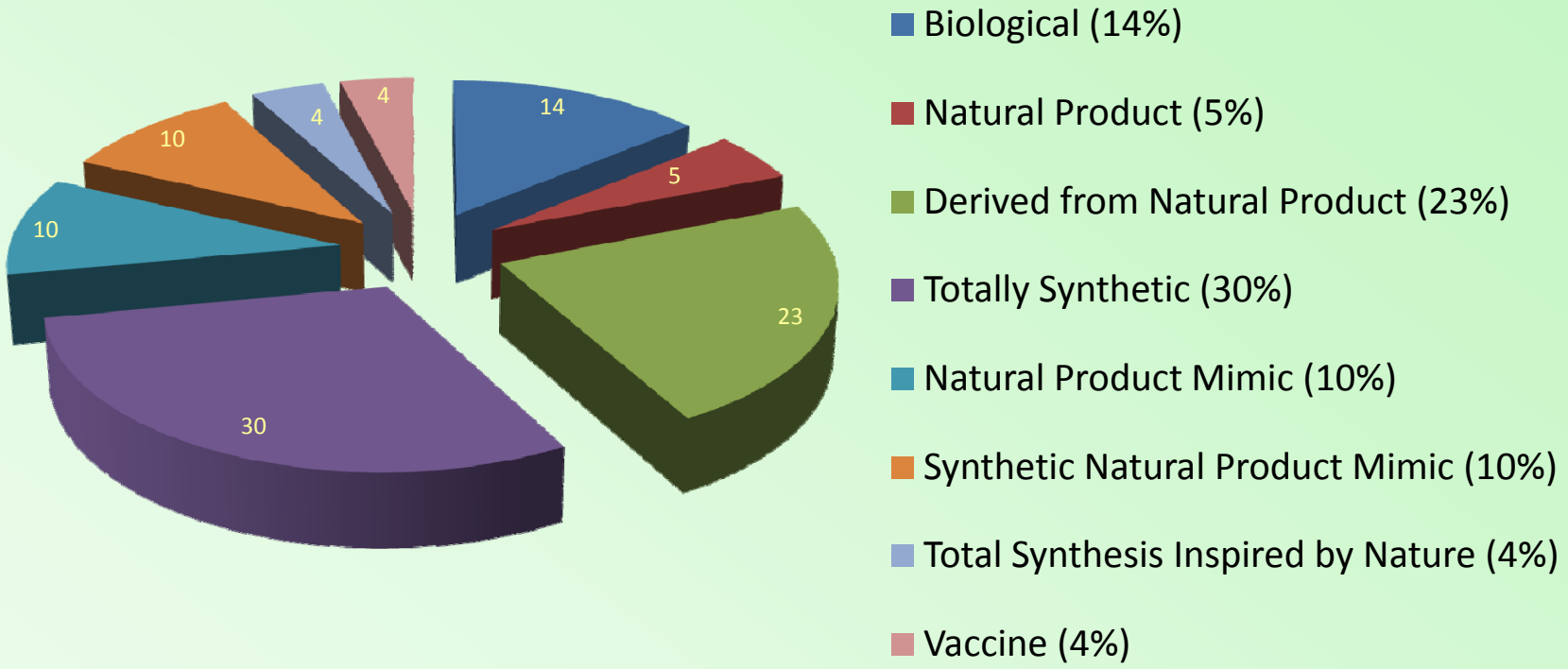
Marticin



Rotenone

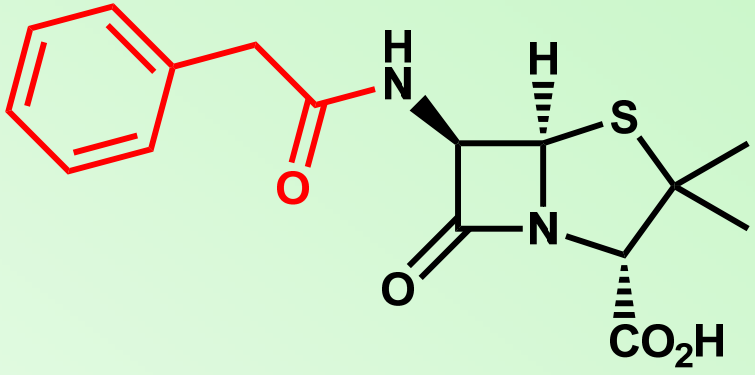
University of the Witwatersrand
South Africa

Origin of Chemical Entities



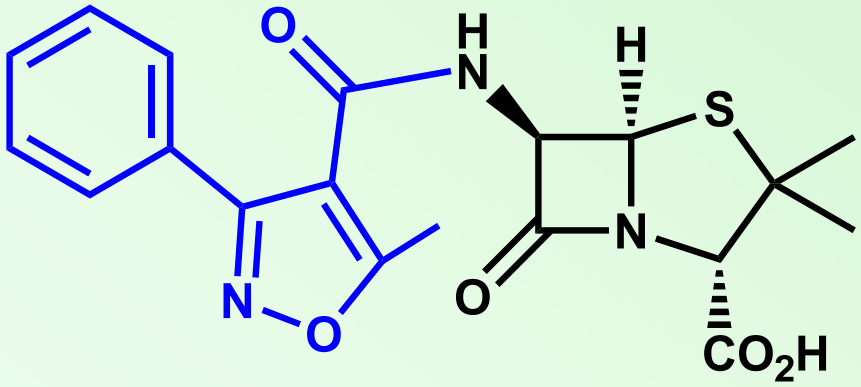
Over past 25 years nearly half of the 1184 new chemical entities that have been marketed come from substances found in Nature

Drugs from Nature— Penicillin



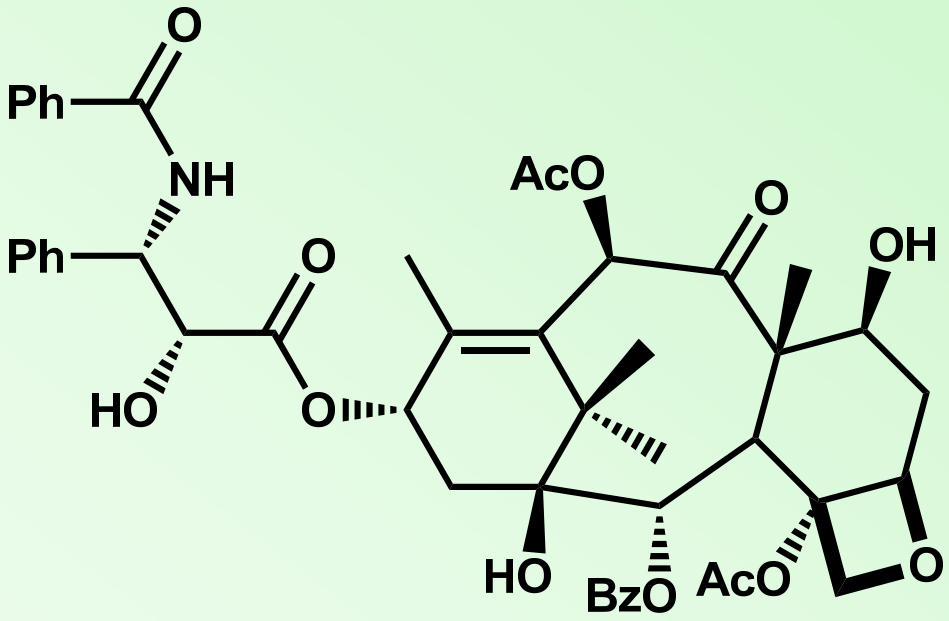
Penicillin G isolated from the mold *Penicillium notatum*

Drugs from Nature—Semi-Synthesis Penicillin

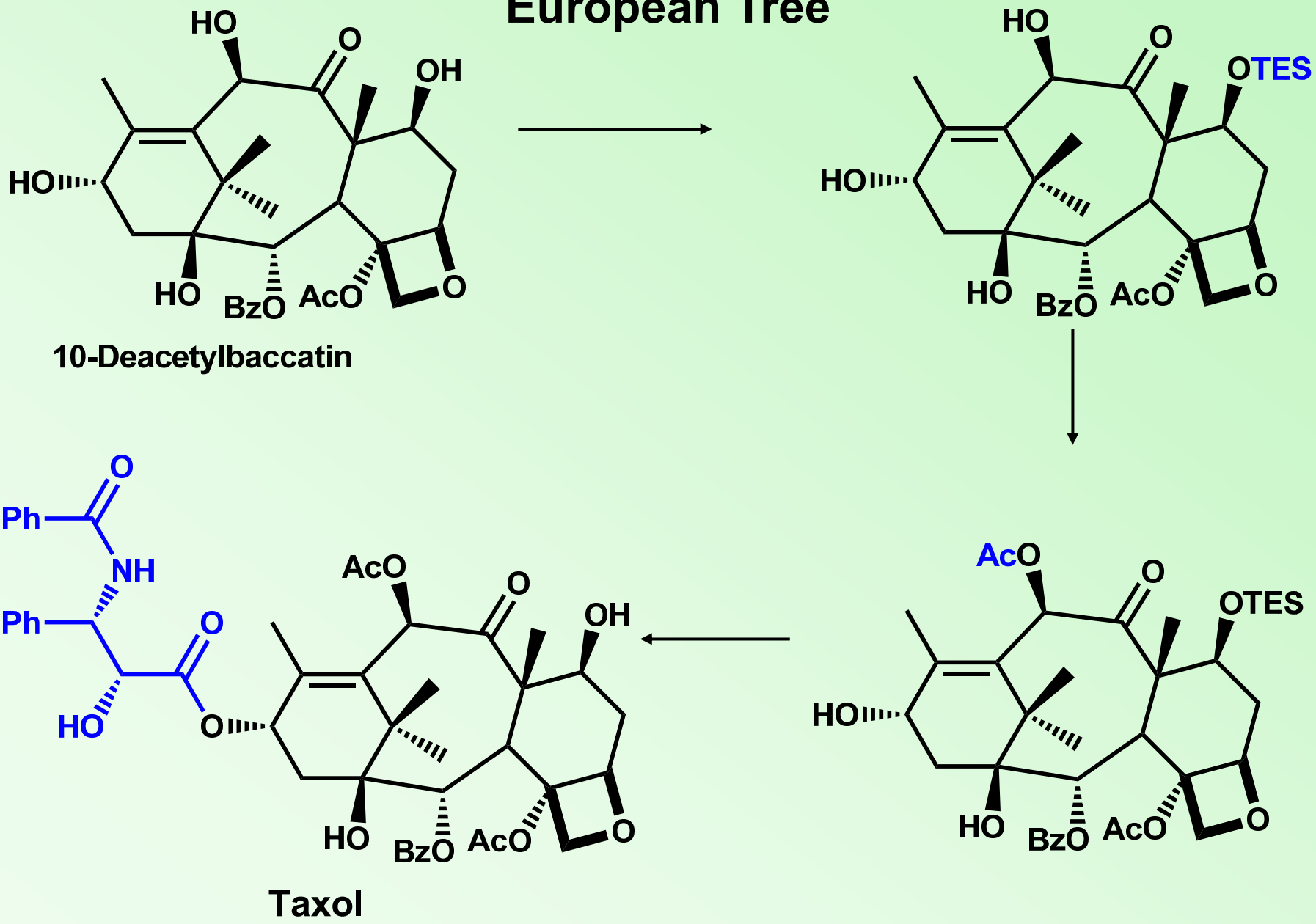


Oxacillin

Anticancer Agent: Drugs from Nature— Taxol

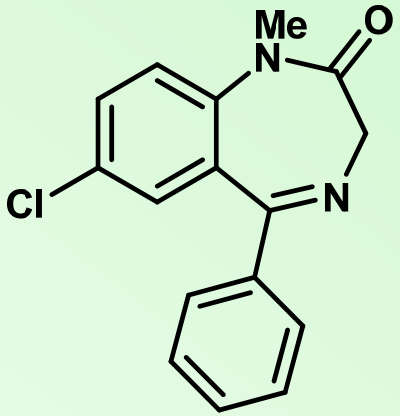


Anticancer Agent: Synthesis from pine needles of European Tree

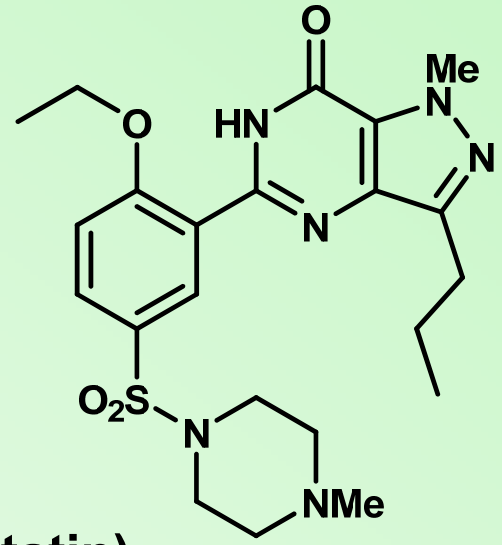


Examples of Synthetic Drugs

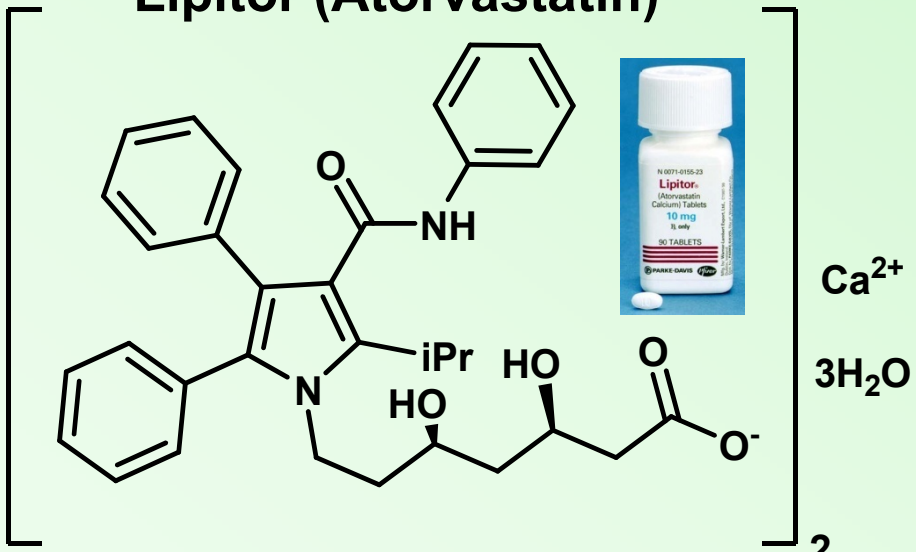
Valium (Daizepam)



Viagra (Sildenafil Citrate)

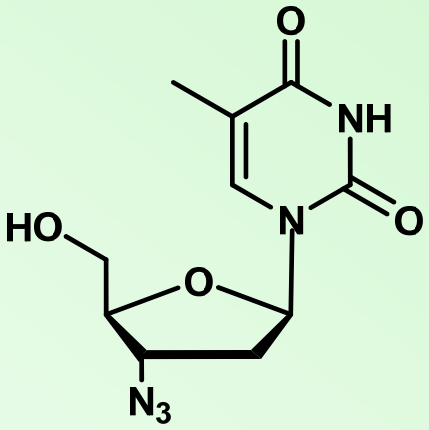


Lipitor (Atorvastatin)

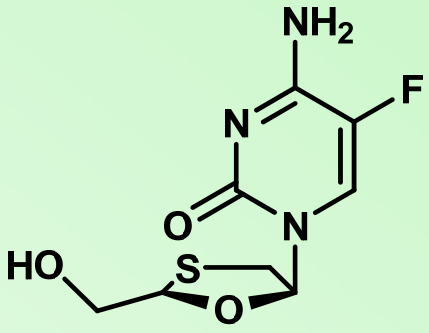


Reverse Transcriptase Inhibitors

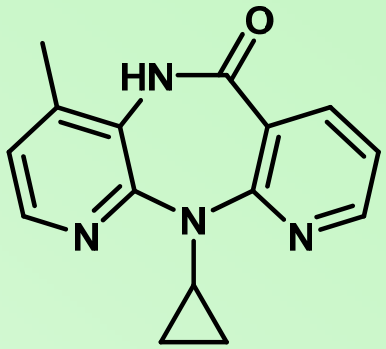
AZT



Emtricitabine (Emtriva)

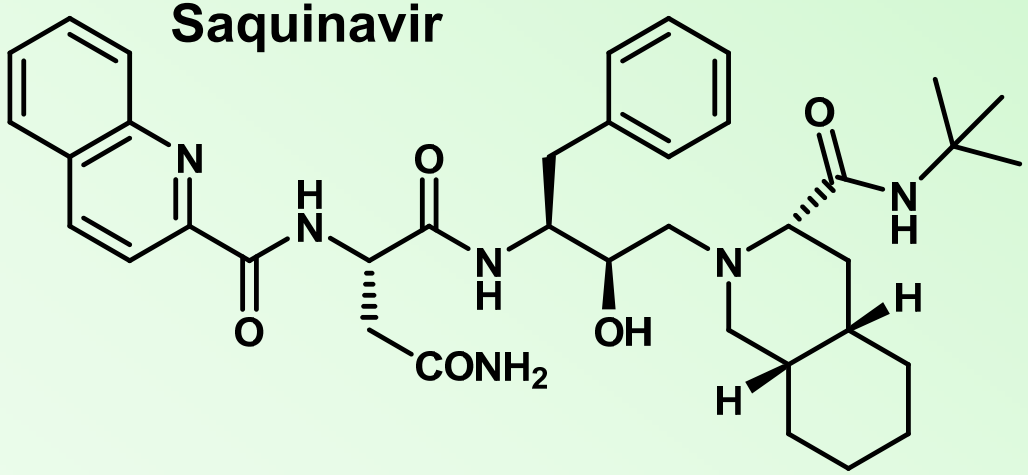


Nevirapine



Protease Inhibitors:

Saquinavir



Two Projects in our Laboratories

- **Natural Product based Project**

Tanzania: four plants used to prolong the life of people infected with HIV

What are the active ingredients?

***Prenacantha kaurabassana* tuber**

Extraction of natural (organic) products by following the bioactivity.

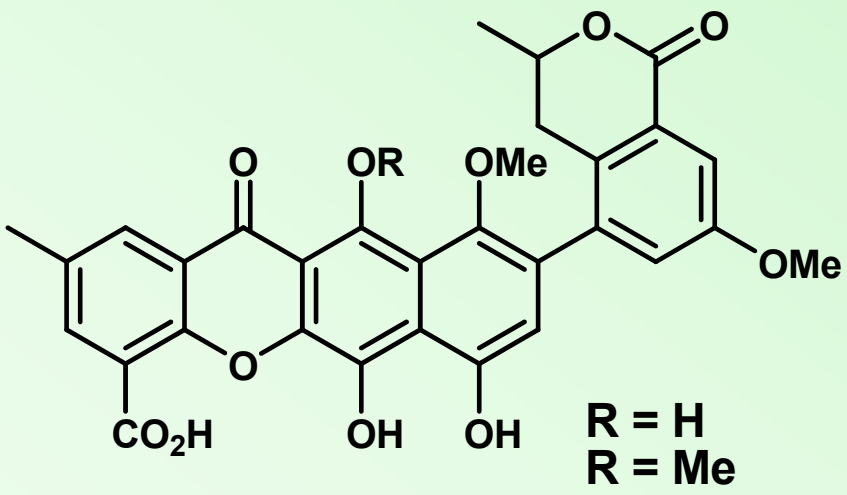
- How do you do this?

- What bioassay do you use?

- Use organic solvent (EtOAc). Extract showed moderate anti-HIV activity as HIV entry inhibitor assay by displaying full inhibition at 25 µg/mL.

- Could be wrong bioassay—might not be entry inhibitor!

Take crude organic solvent (EtOAc) that showed moderate anti-HIV activity and try to purify mixture.



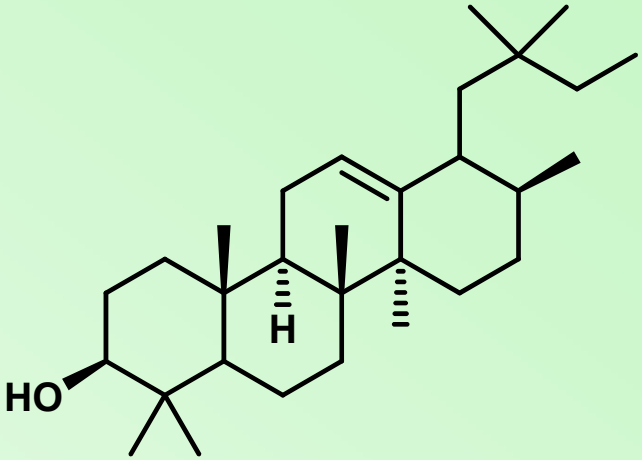


Table 4. HIV Screening Results of Xanthones **1** and **2** in the deCIPhR® Assay
IC_{50} = 50% inhibitory concentration in anti-HIV assay; TC_{50} = 50% inhibitory concentration in cytotoxicity assay

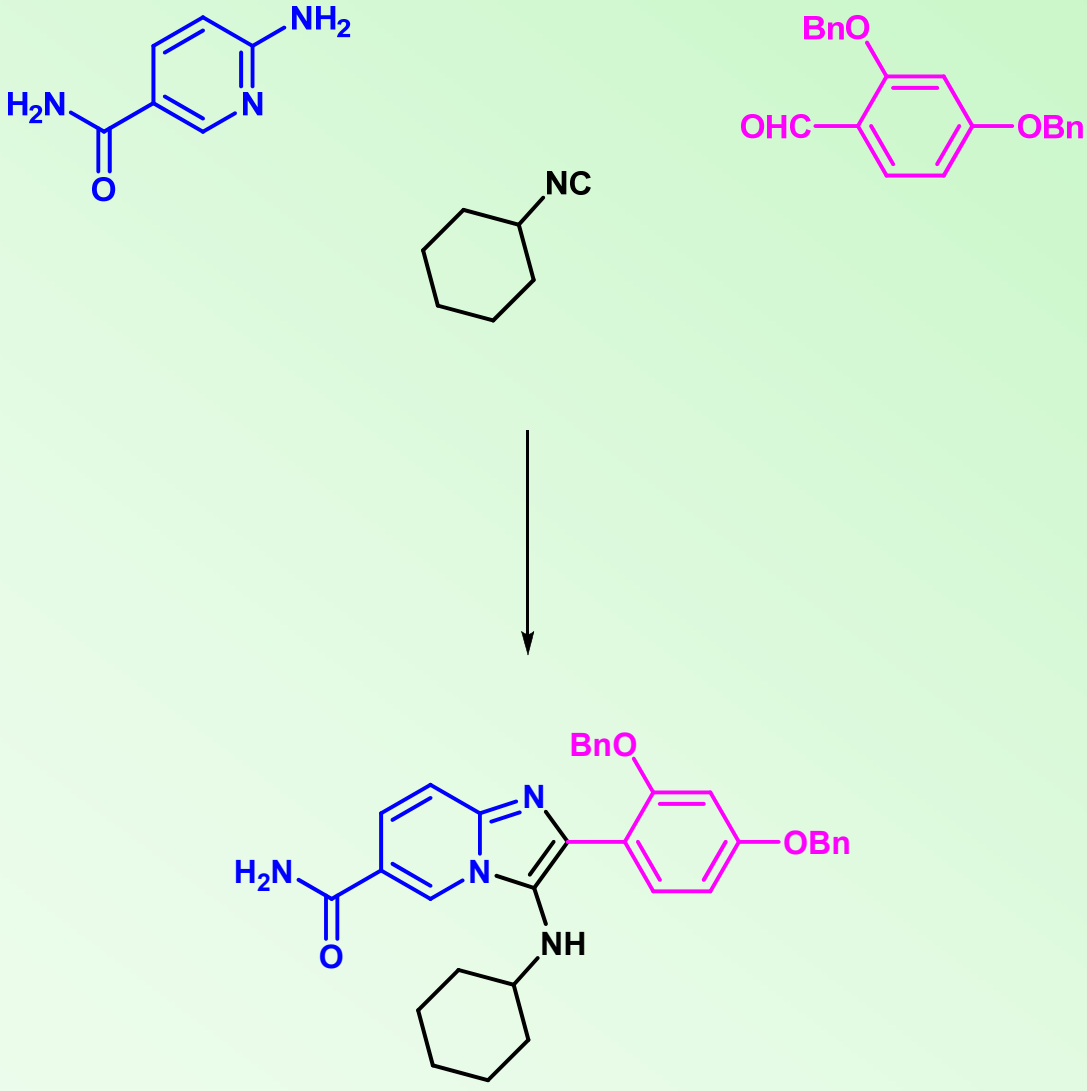
Sample	**IC_{50} (µg/mL)**	**TC_{50} (µg/mL)**	**SI**	**IC_{90} (µg/mL)**	**TC_{90} (µg/mL)**	**SI**
Xanthone **1**	21	>12.5	-	111	>12.5	-
Xanthone **2**	2	31	15.5	22	154	7
Enfuvirtide (positive control)	0.01	Not done	-	0.026	Not done	-

A Bioassay Guided Investigation of the Tanzanian plant *Pyrenacantha kaurabassana Baill* for Potential anti-HIV active Compounds, J J Omolo, V Maharaj, D Naidoo, T Klimkait, H M Malebo, S Mtullu, H V M Lyaruu and C B de Koning, accepted in *Journal of Natural Products*, September 2012.

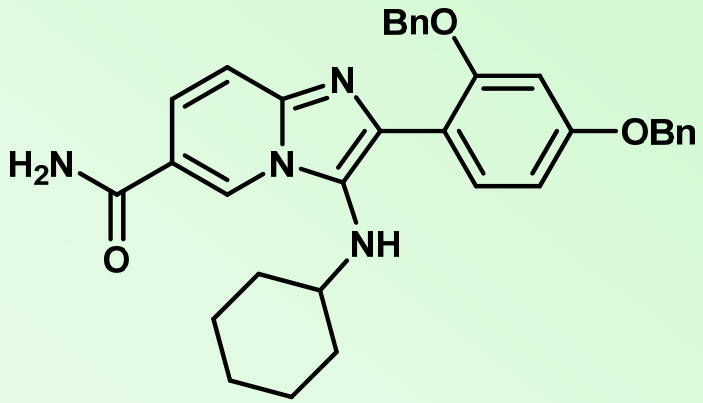
NMR Spectroscopy Facility

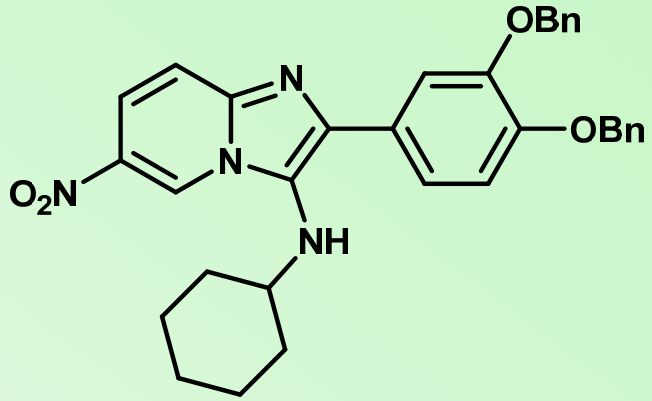
R8 million
Needs liquid argon and nitrogen

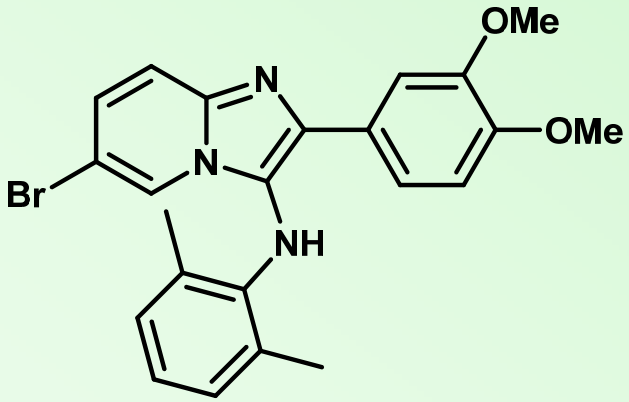
Synthesis based Project



Synthesis based Project







Study their activity against diseases

Colon Cancer---Caco 2 and HT 29 cell lines

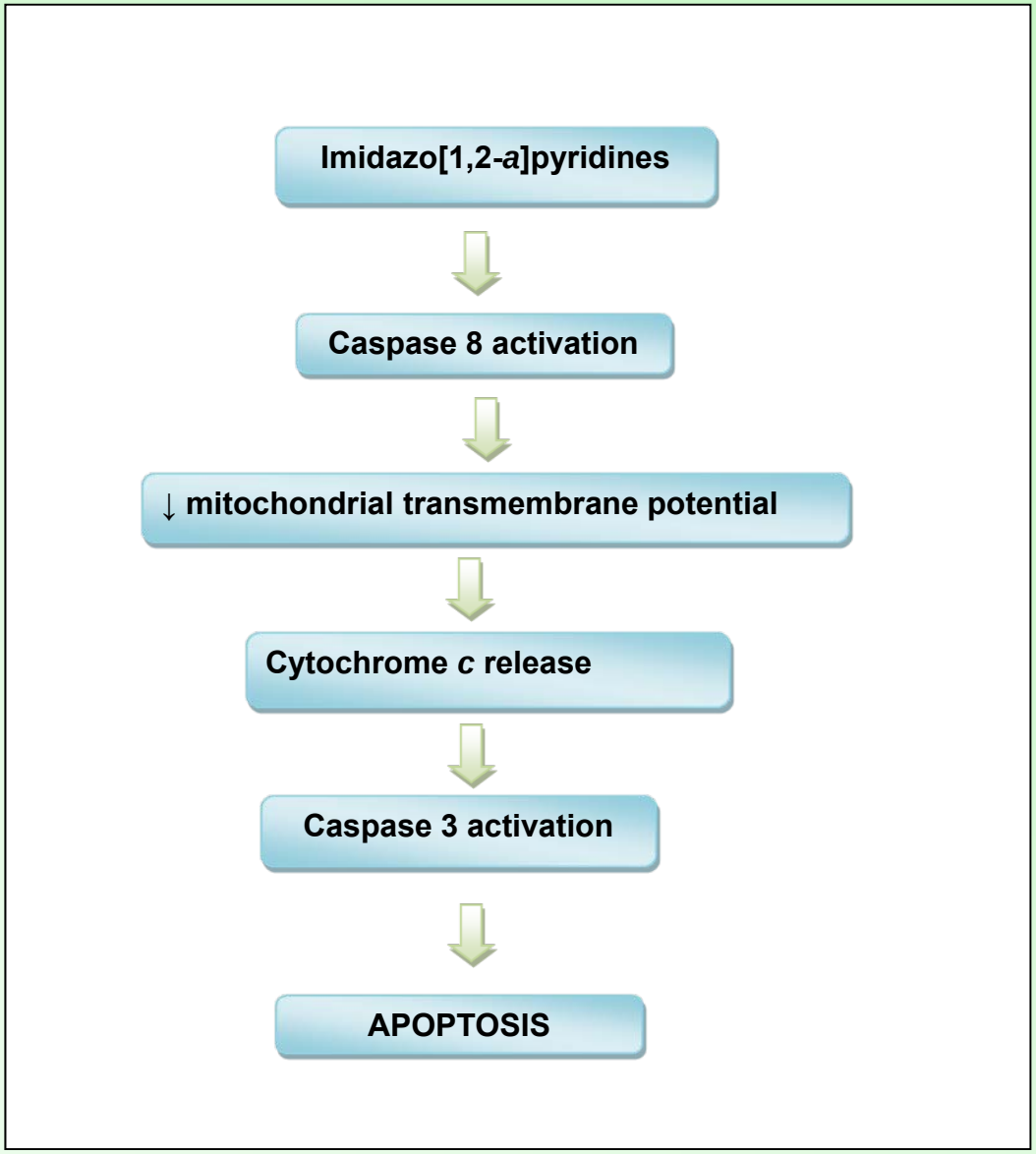
Work out their mechanism of action

Compounds were found to be very active against colon cancer and not toxic to white blood cells

	IC_{50} (μM)	
Compound	**HT-29**	**Caco-2**
3	12.89 ± 2.41	11.91 ± 1.10
4	6.57 ± 1.91	6.43 ± 1.01
6	9.14 ± 1.02	9.03 ± 0.99
7	9.20 ± 0.83	17.38 ± 1.13
12	21.98 ± 1.17	20.28 ± 3.45
13	10.03 ± 2.69	15.02 ± 1.98
14	8.56 ± 1.22	8.73 ± 1.28
Camptothecin	10.00 ± 1.41	9.55 ± 2.21

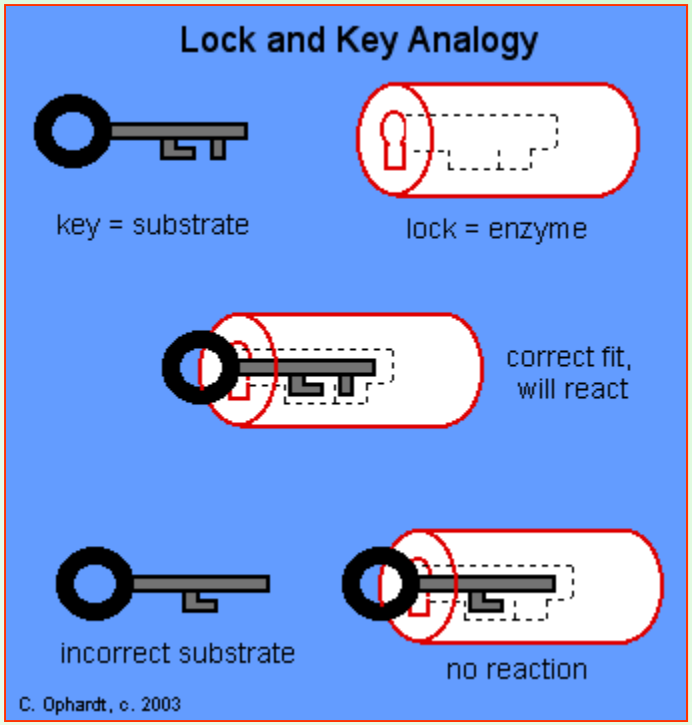
Compound	IC_{50} (μM) HT-29	Caco-2
3	12.89 ± 2.41	11.91 ± 1.10
4	6.57 ± 1.91	6.43 ± 1.01
6	9.14 ± 1.02	9.03 ± 0.99
7	9.20 ± 0.83	17.38 ± 1.13
12	21.98 ± 1.17	20.28 ± 3.45
13	10.03 ± 2.69	15.02 ± 1.98
14	8.56 ± 1.22	8.73 ± 1.28
Camptothecin	10.00 ± 1.41	9.55 ± 2.21

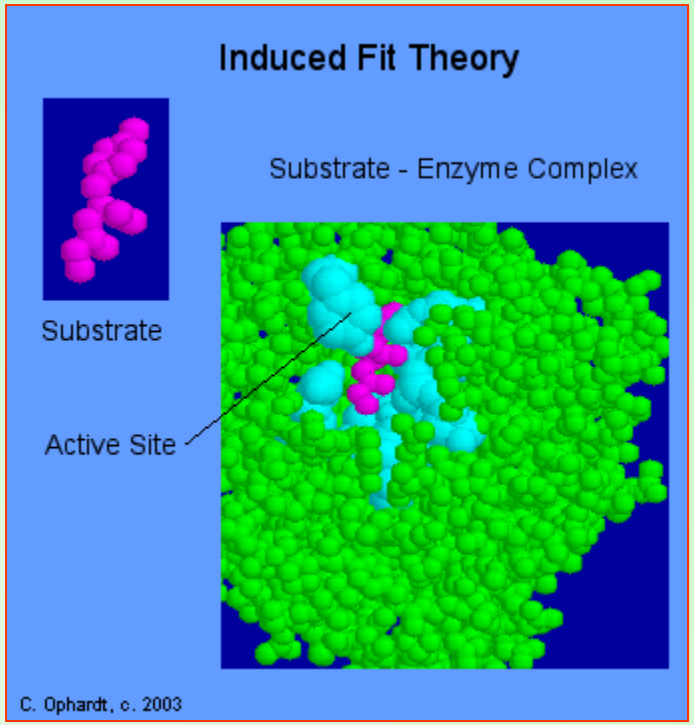
Compound	White Blood Cell Viability %
3	76.176 ± 0.567 %
4	88.943 ± 1.996 %
6	83.762 ± 1.389 %
7	93.834 ± 0.271 %
12	96.311 ± 5.023 %
13	97.479 ± 1.178 %
14	77.345 ± 1.005 %
Camptothecin	33.782 ± 2.031 %



6-Substituted Imidazo[1,2-*a*]pyridines: Synthesis and Biological Activity Against Colon Cancer Cell Lines HT-29 and Caco-2, N Dahan-Farkas, C Langley, A L Rousseau, D B Yadav, H Davids and C B de Koning, *European Journal of Medicinal Chemistry*, 2011, 46, 4573-4583.

Targets for Drugs often Enzymes/Proteins:



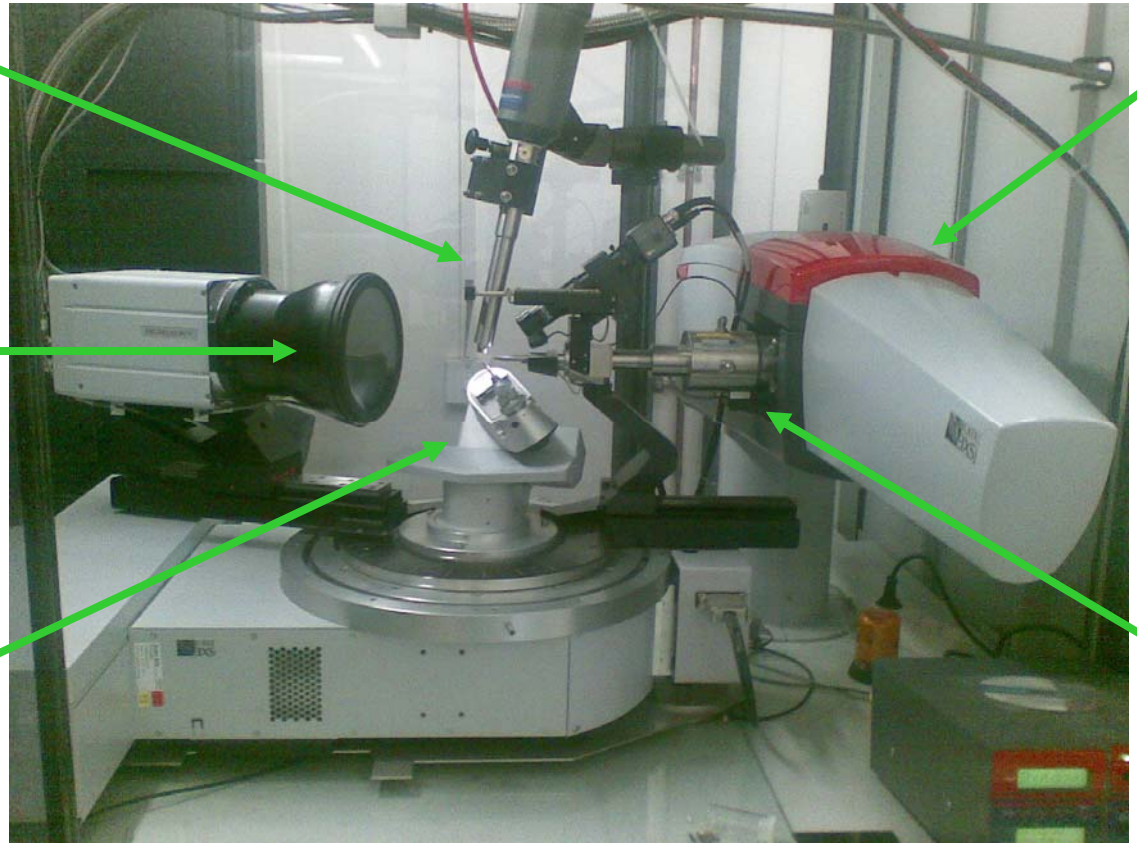


The X8 Diffractometer

80- 500 K Oxford Cryostream Plus system

4K Platinum 135 CCD detector

Four-axis Kappa goniometer



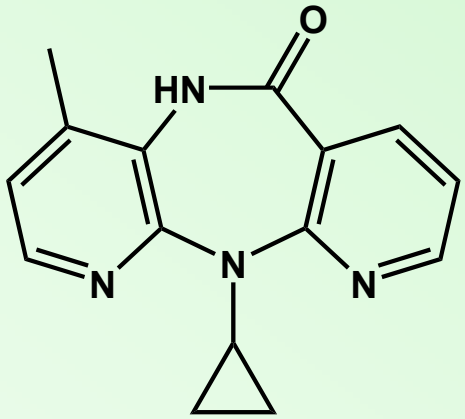
2.7 kW Microstar Cu rotating-anode generator

λ = 1.54178 Å

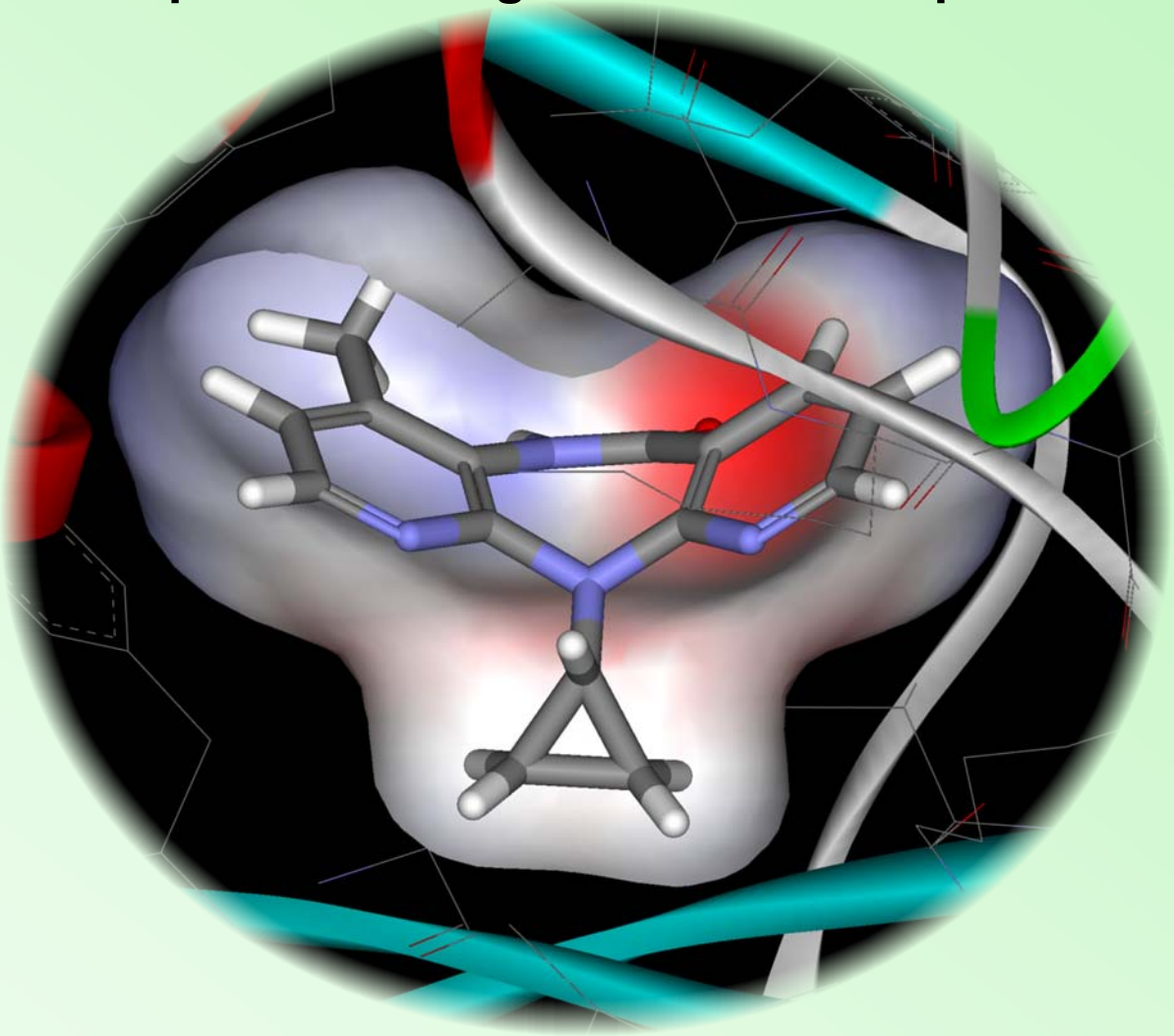
Montel optics

Anti-HIV drugs

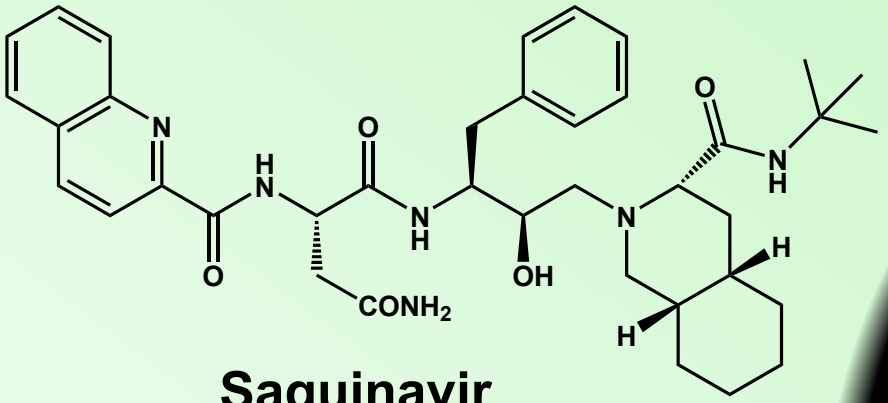
Crystal structure of nevirapine inhibiting reverse transcriptase



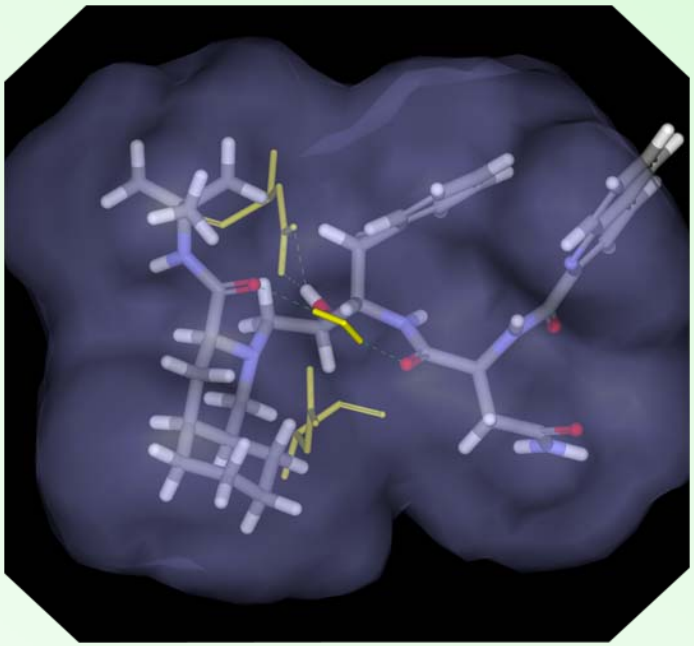
Nevirapine (Viramune)

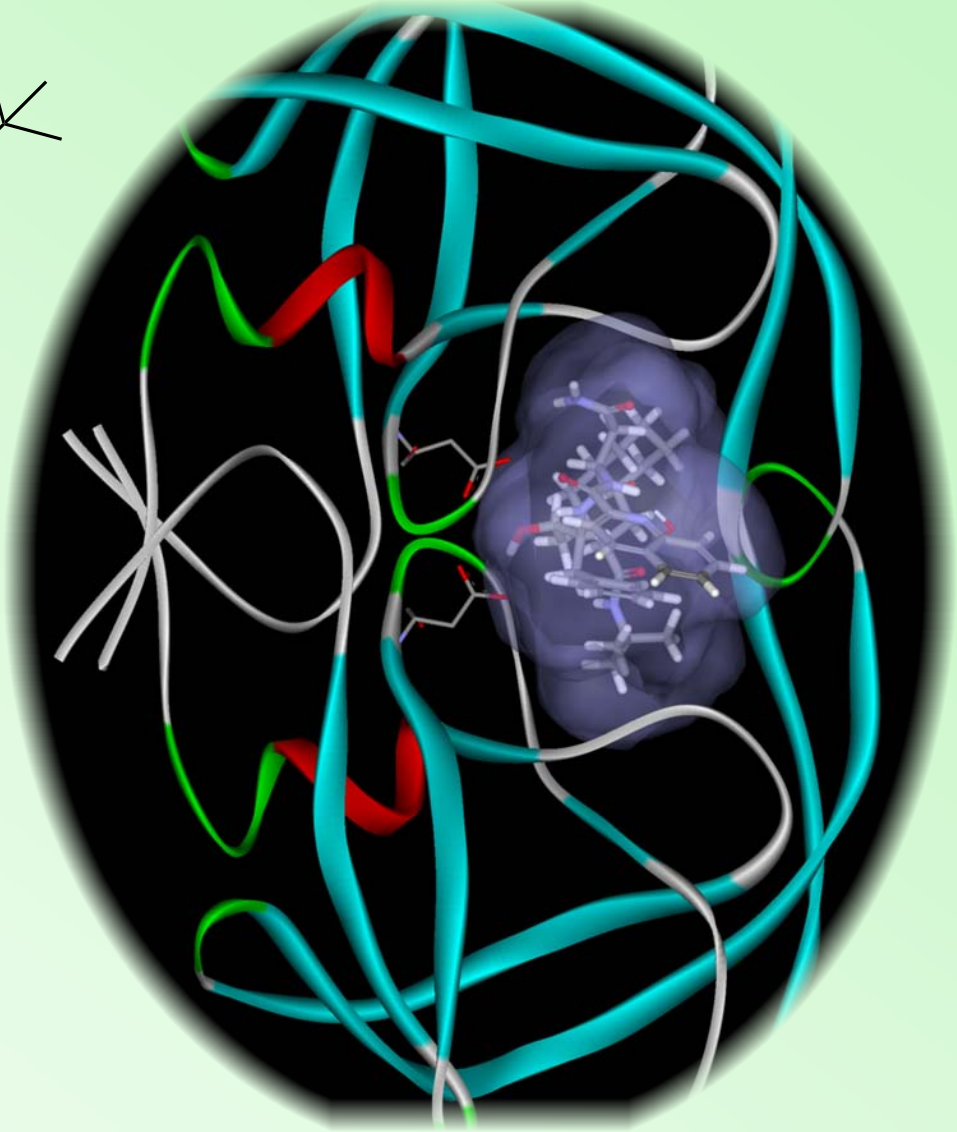


Anti-HIV drugs
Crystal structure of saquinavir inhibiting HIV protease



Saquinavir
(Invirase)



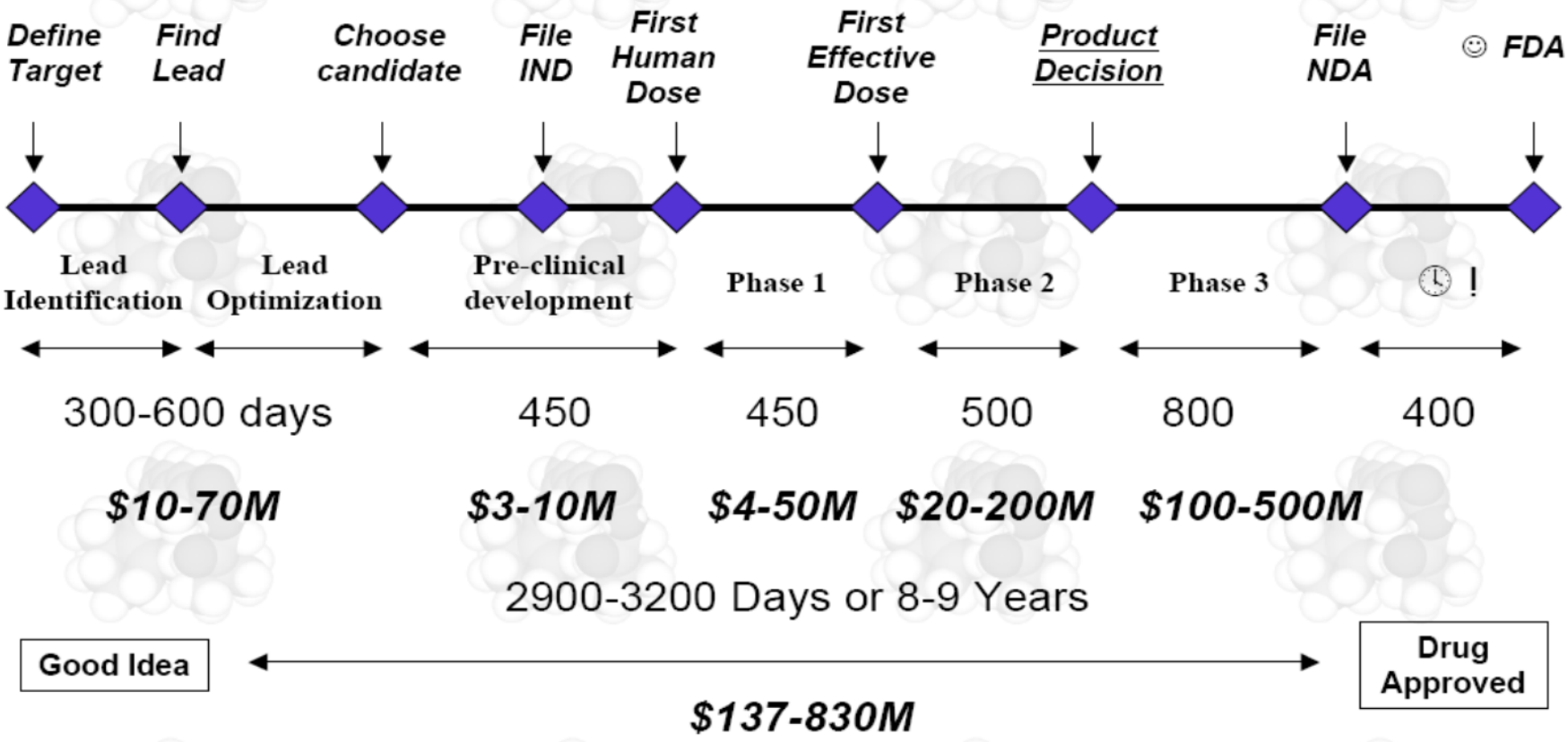


- **Natural Products are important compounds for discovery of medicines**

- **Natural product isolation combined with synthesis allows for assembly of new biologically chemical entities**

- **Universities can do basic research such as isolation, synthesis, identifying biological targets, preliminary biological testing**

Drug R&D in Review



Oh, and there is roughly a 4% chance of success

"Half of the modern drugs could well be thrown out of the window, except that the birds might eat them."
Martin Henry Fischer: