Drugs for 3rd World Diseases: The Good, the Bad, and the Ugly

Richard Elliott

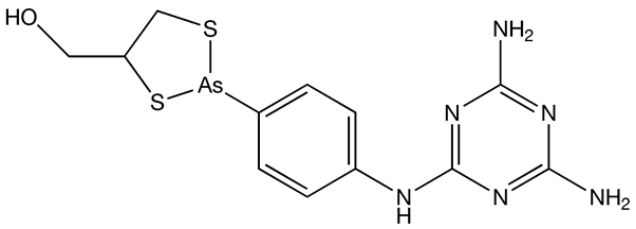
4th Annual CDD Community Meeting

Oct 21, 2010

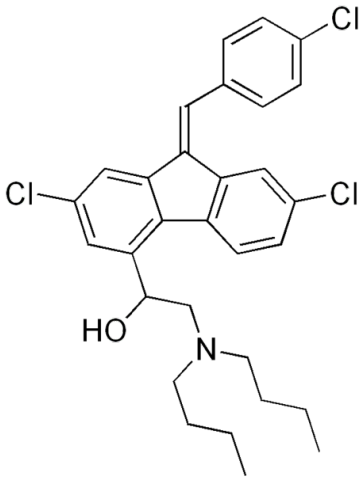
BILL & MELINDA GATES foundation

The Good, the Bad, and the Ugly

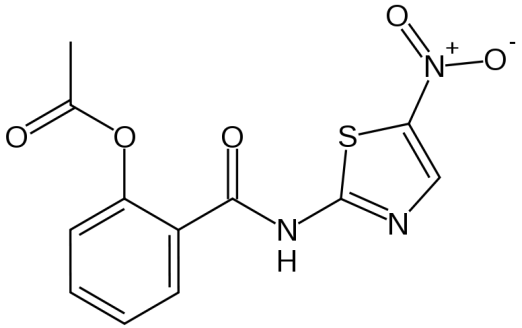
The Ugly Tuco (Eli Wallach)



Melarsoprol



Lumefantrine



Nitazoxanide

How do you define an ugly molecule?

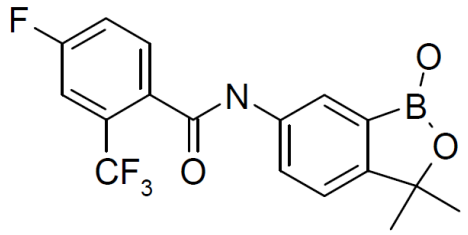
What do we really mean when we say a molecule is “ugly”?

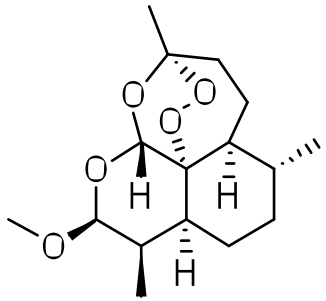
Can we really tell is a molecule is ugly just by looking at it?

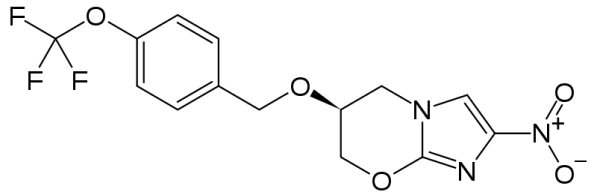
The unsavory nature of 3rd world disease drugs

GRC Medicinal Chemistry Meeting, August 8-13, 2010; Colby-Sawyer College

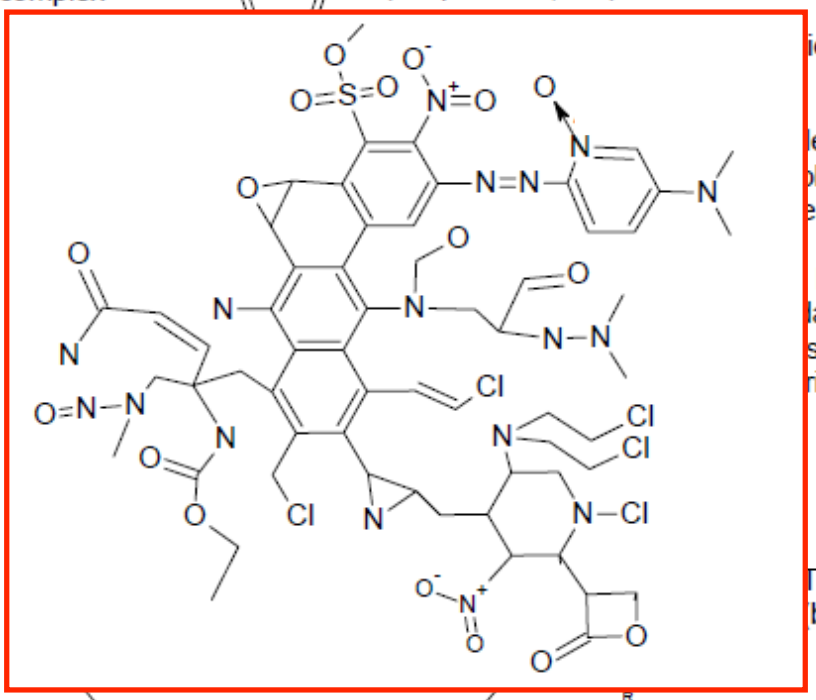
7:30 pm - 9:30 pm	**THIRD WORLD DISEASES**
	Discussion Leader: **Richard Elliott** (Bill and Melinda Gates Foundation)
7:30 pm - 8:00 pm	**Robert T. Jacobs** (Scynexis) "Discovery and Pre-Clinical Development of SCYX-7158 (AN 5568), a Novel Oxaborole-6-Carboxamide with Potential for Treatment of Stage 2 Human African Trypanosomiasis"
8:00 pm - 8:10 pm	Discussion
8:10 pm - 8:40 pm	**Jeremy Burrows** (MMV) "Antimalarial Medicinal Chemistry: challenges & opportunities"
8:40 pm - 8:50 pm	Discussion
8:50 pm - 9:20 pm	**Clifton Barry III** (NIH) "Antitubercular nitroimidazoles: structure-based approaches to optimization of a prodrug"
9:20 pm - 9:30 pm	Discussion







Some Common Structural Alerts



Dioxolanes – P450 MI complex

furan – furosemide, ipomeanol (but prazosin, OK)

id, ticlopidine

Quinoxaline N-oxides - carbadox

le – thiabendazole or aminothiazole
le conversion to thioamides,
eas (but famotidine OK)

Polyheteroaromatics, often 1A substrates – example shown

P450 inhibition, thiazole – ritonavir
lazole – cimetidine; also
stituted imidazoles – ketoconazole,
rimazole (but famotidine OK)

Alkyl substituted indoles, pyrroles – 3-methylindole

Diphenylamine in ring, e.g. carbamazepine, or not, e.g. diclofenac

(ring)

Thiazolidinediones - troglitazone
but rosiglitazone, pioglitazone OK)

Various tricyclics that can form arene oxides or reactive imines e.g.amineptine

N-phenylsuccinimides – some are nephrotoxic

Radical formation – phenytoin (cf thalidomide)

Quinolines when R_1 & R_2 =H (but saquinavir, R_1 = alkyl, OK)

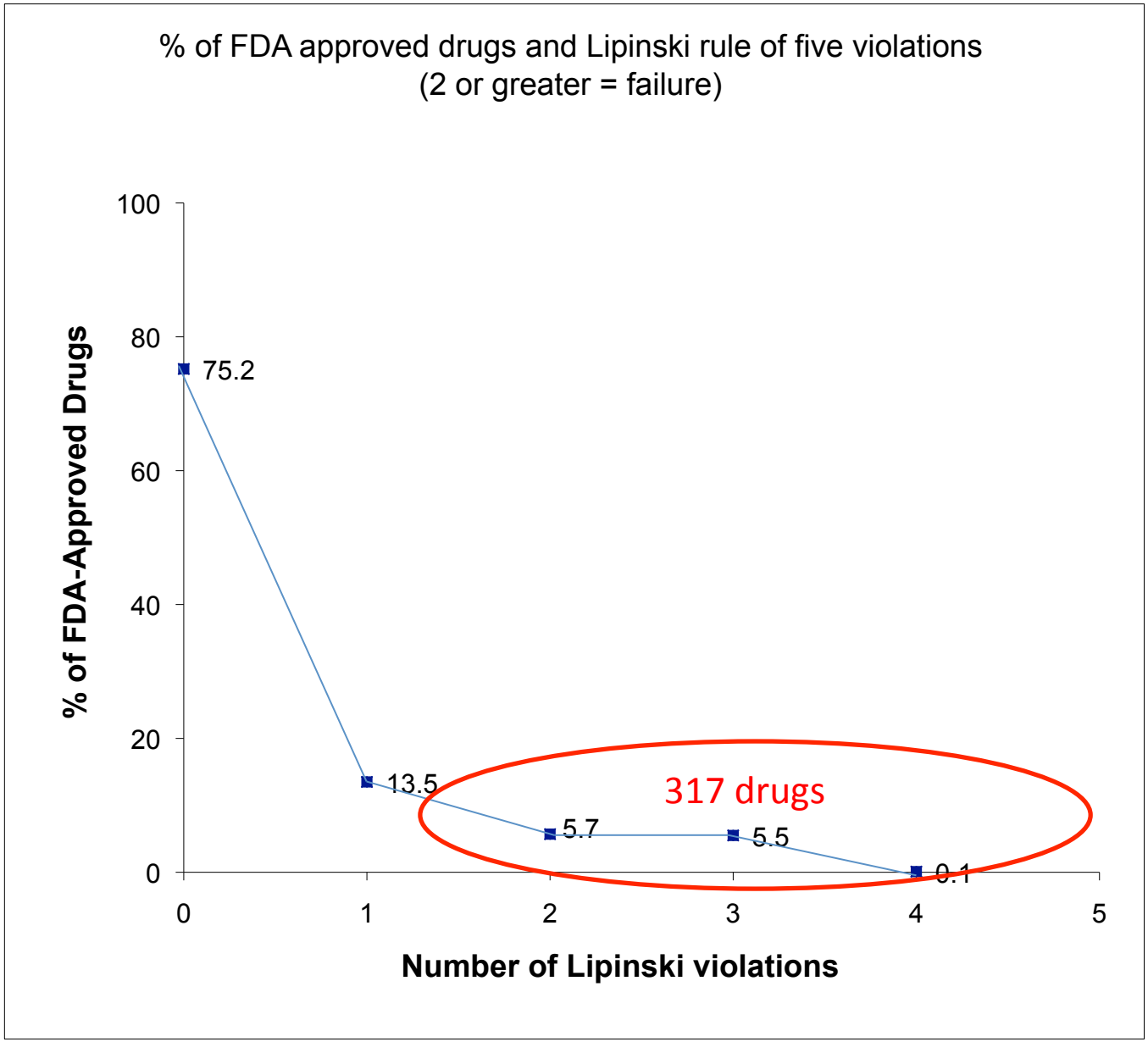
Unsaturated piperidines, piperazines, dihydroquinolines or hydroxy precursors – MPTP, haloperido, mianserin ketoconazole

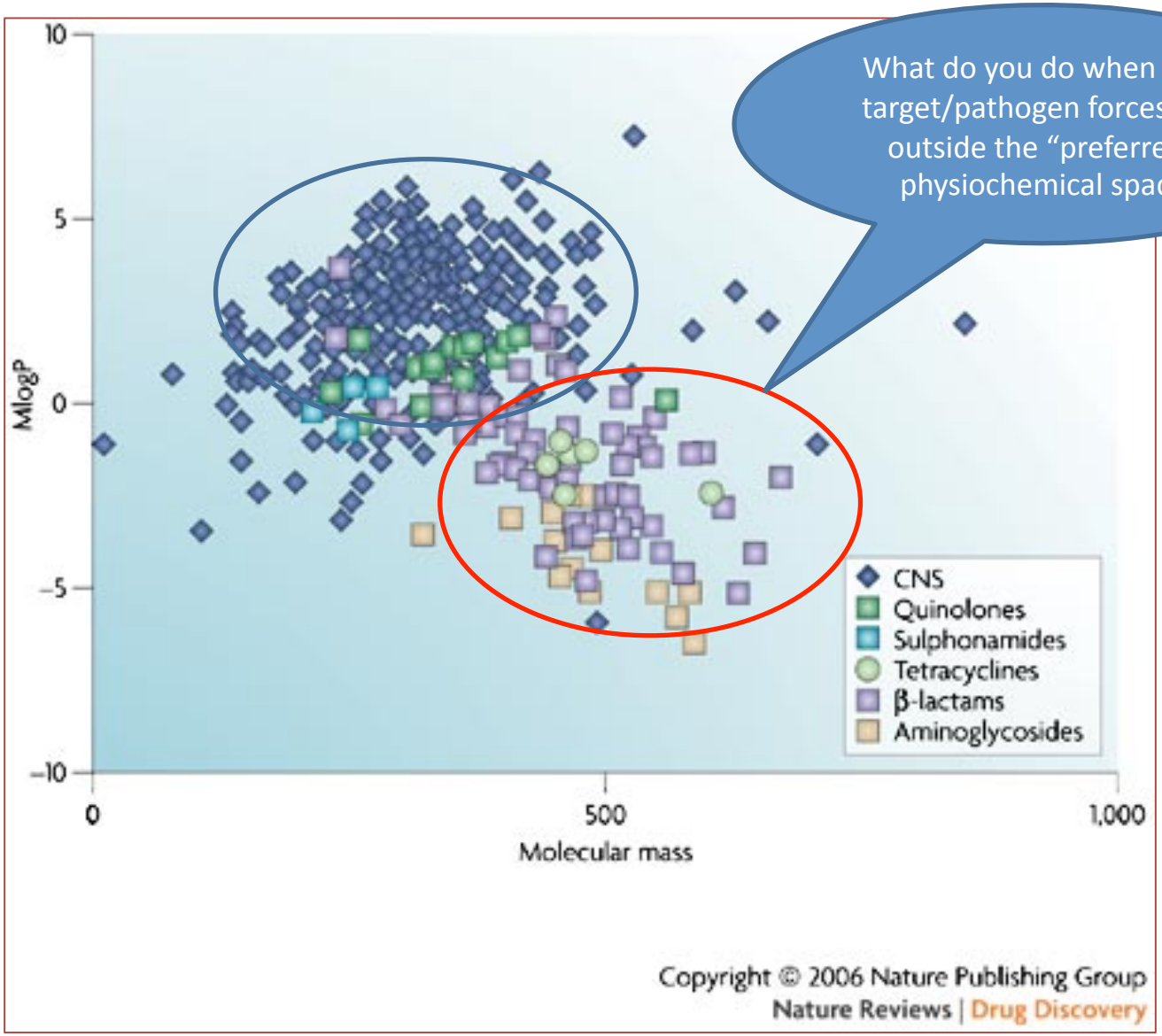
Lipinski's Rule-of-Five

Lipinski's rule says that, in general, an orally active drug has no more than one violation of the following criteria:

- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular weight under 500 daltons
- An octanol-water partition coefficient log P of less than 5

Are structural alerts/Lipinski rule's really the best to say if a molecule is ugly? How well do these rules work for third-world drug discovery


% of FDA approved drugs and Lipinski rule of five violations
(2 or greater = failure)
% of FDA-Approved Drugs
100
80
60
40
20
0
75.2
13.5
5.7
5.5
0.1
317 drugs
0
1
2
3
4
5
Number of Lipinski violations



Payne *et al. Nature Reviews Drug Discovery* **6**, 29–40 (January 2007)

CORANTE

Home > Weblog Columns > In the Pipeline

In the Pipeline: Don't miss Derek Lowe's excellent commentary on drug discovery and the pharma industry in general at **In the Pipeline**

ABOUT THIS AUTHOR

Derek Lowe, an Arkansan by birth, got his BA from Hendrix College and his PhD in organic chemistry from Duke before spending time in Germany on a Humboldt Fellowship on his post-doc. He's worked for several major pharmaceutical companies since 1989 on drug discovery projects against schizophrenia, Alzheimer's, diabetes, osteoporosis and other diseases. To contact Derek email him directly: derekb.lowe@gmail.com
Twitter: Dereklowe

Chemistry and Drug Data: Drugbank

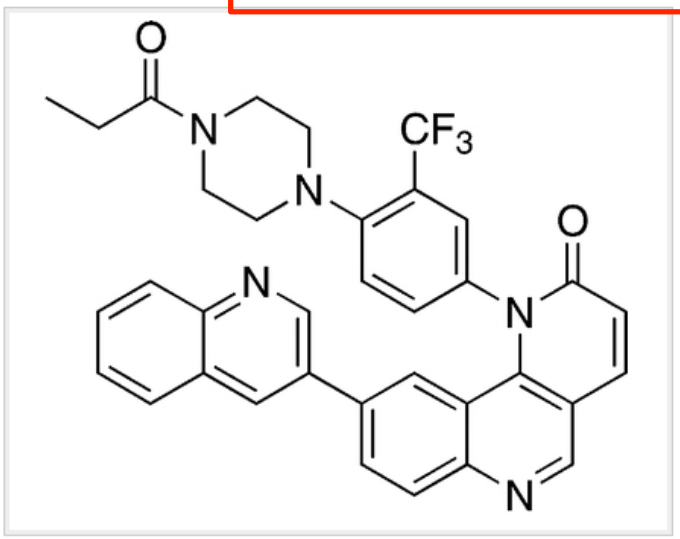
In the Pipeline

September 23, 2010

Delightful, But It Apparently Works

Posted by **Derek**

And I now present today's winner of the Ugliest Molecule To Actually Show In Vivo Efficacy. Here, just in time for lunch, is Torin-1, a selective mTOR inhibitor. Yowza.



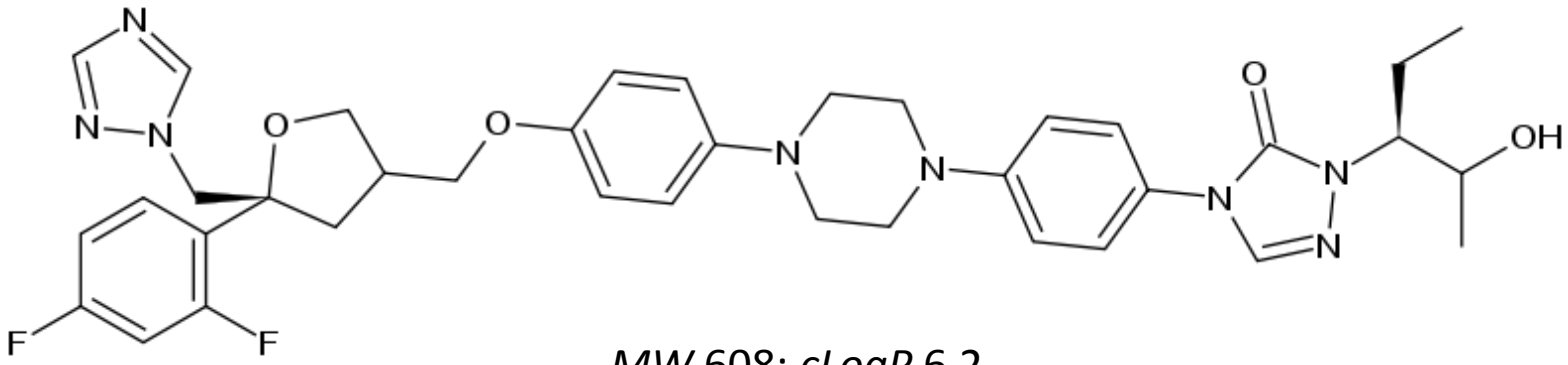
Comments (17) + TrackBacks (0) | Category: Chemical News

Grayscale Rainbow on September 23, 2010 12:30 PM writes... Oh, come on Derek, fess up. You know somewhere in your career you've made a compound or two (or more) with a MW~600 and cLogP ~6, which weren't even active in vitro, much less in vivo. Most of us have but we're too ashamed to admit it, unless of course one of them is in the clinic.

Mark on September 23, 2010 1:43 PM writes... My question is, what color is it?

Milkshake on September 23, 2010 12:35 PM writes... I think this one still has some solubility left because there are no free NH in the molecule. For another horrific example of an oral drug design, see itraconazole and posaconazole

Posaconazole



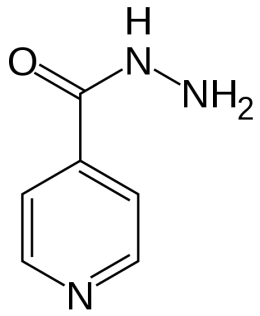
MW 608; *cLogP* 6.2

%F = >90% (food effect); $T_{1/2}$ = 35 hours

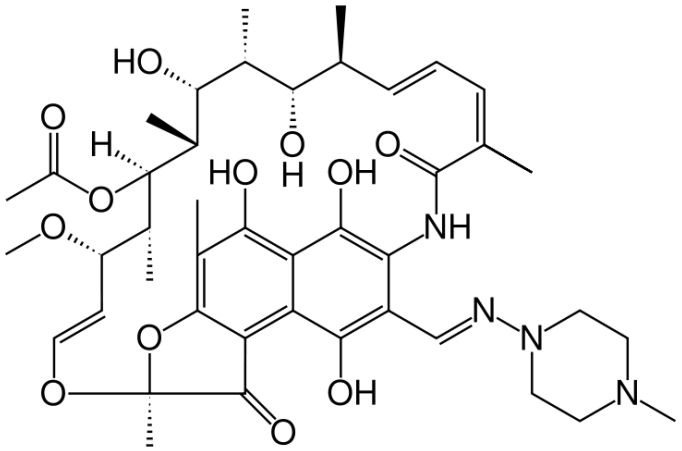
Posaconazole, initially available as an oral solution, was launched in European markets after gaining its first country approvals in December 2005; US FDA approval was received in September 2006 and analysts predict total sales of $500 million in 2010.

Merck entering Phase II studies for Chagas Disease
http://www.merck.com/newsroom/news-release-archive/research-and-development/2010_0624.html

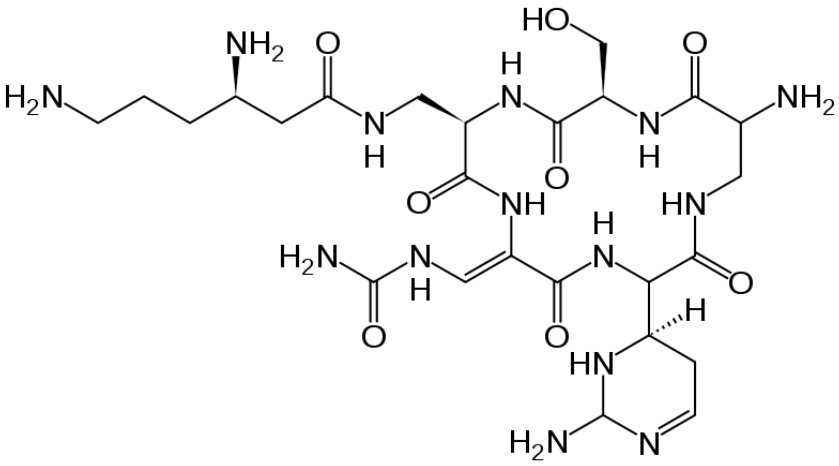
TB Drugs



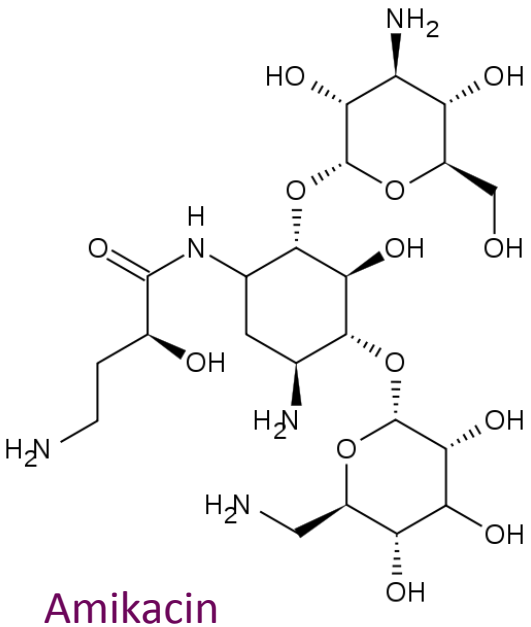
Isoniazid



Rifampin

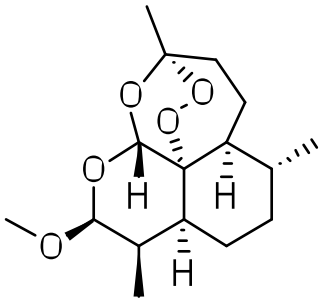


Capreomycin

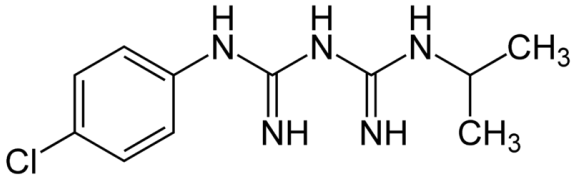


Amikacin

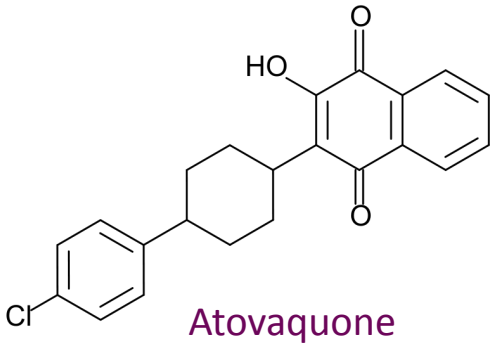
Anti-Malarial Drugs



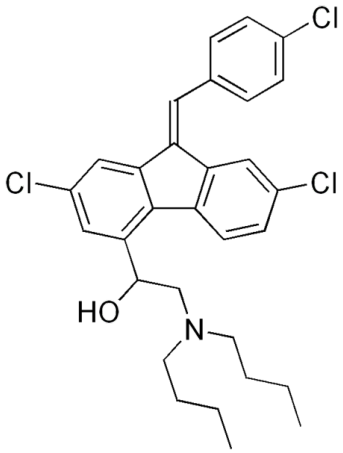
Artemisinin



Proguanil



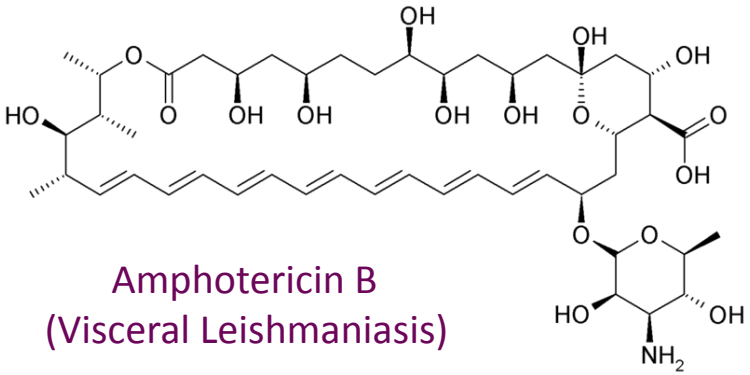
Atovaquone



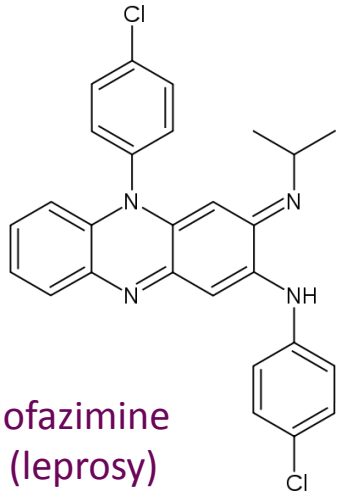
Lumefantrine

From 13,500 GSK hits <1uM, average MWt 446 and clogP 5 (*cf* collection with average MWt 385 and clogP 3.3; [Gamo, F.-J. *et al,* Nature, **2010**, *465*, 305]

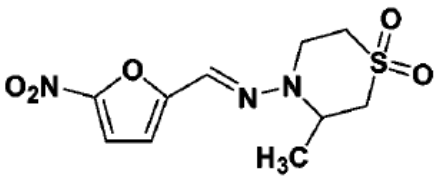
Other 3rd World Drugs



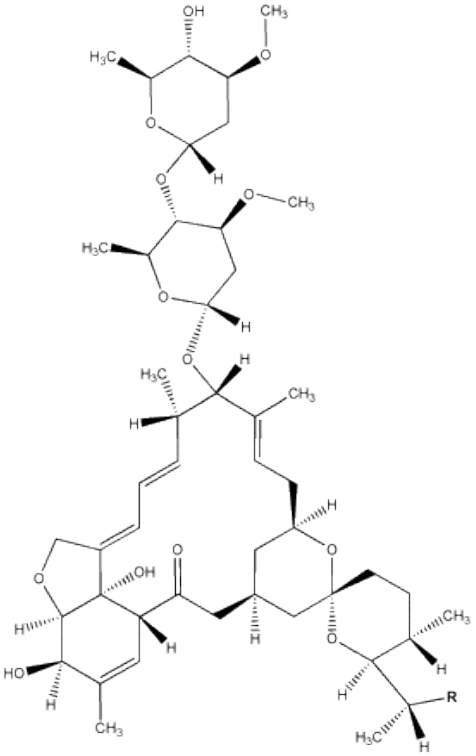
Amphotericin B
(Visceral Leishmaniasis)



Clofazimine
(leprosy)



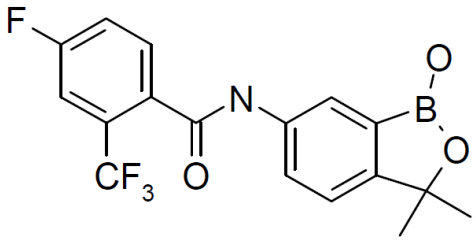
Nifurtimox
(Chagas, HAT)



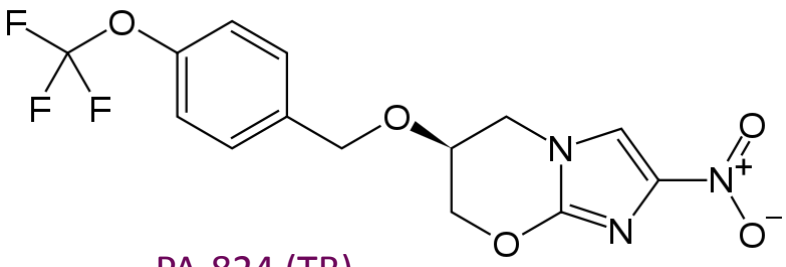
Ivermectin
(LF, Oncho)

But these are older drugs, what about the discovery pipeline?

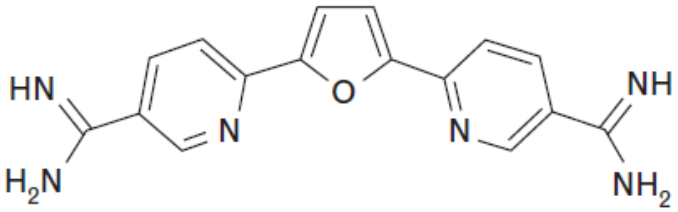
What about our Discovery Pipeline of 3rd World Disease Drugs?



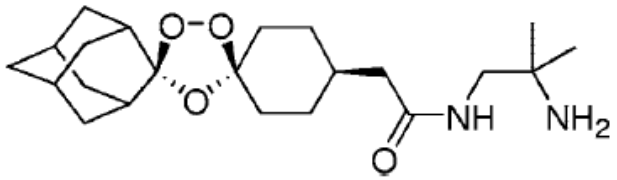
SCYNX-7158 (HAT)



PA-824 (TB)



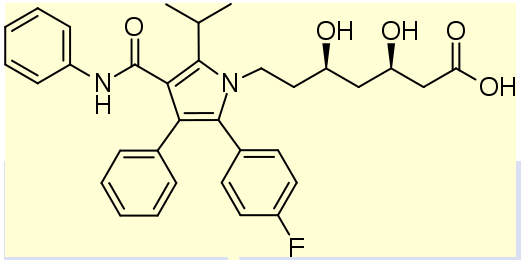
CPD-0802 (HAT)

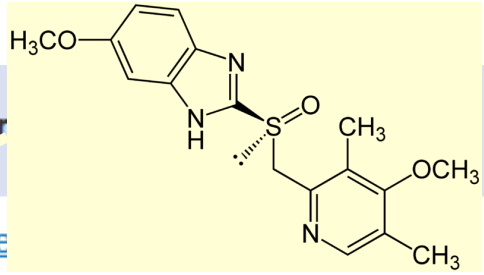


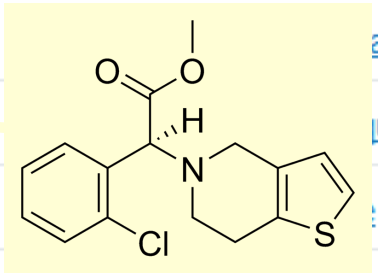
OZ-277 (Malaria)

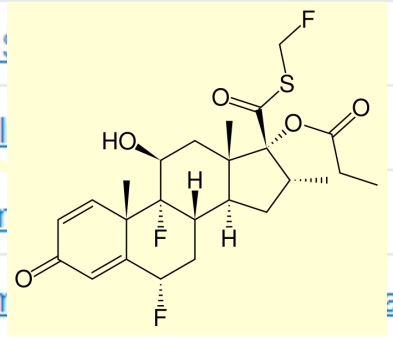
What about 1st world disease drugs?

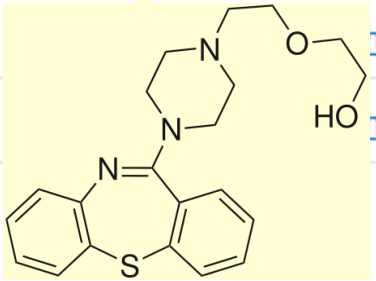
Pharmaceutical Sales 2009











		Curr	Total Sales ($000)	% change 2008
1	Lipitor	Pfize	5,363,193	-8.8%
2	Nexium	armaceuticals	5,014,827	4.6%
3	Plavix	uibb Company	4,223,124	11.2%
4	Advair Diskus		3,653,410	2.3%
5 (↑1)	Seroquel	AstraZeneca Pharmaceuticals	3,117,591	7.2%
6 (↑6)	Abilify	Bristol-Myers S	3,083,351	30.0%
7	Singulair	Merck & Co., I	3,027,378	4.5%
8 (↑1)	OxyContin	Purdue Pharm	3,020,239	20.7%
9 (↑1)	Actos	harm a, Inc	2,531,621	3.4%
10 (↓5)	Prevacid	harmaceuticals North America, Inc	2,508,555	-23.9%
			35,543,289	

http://www.drugs.com/top200.html

Some Basic Questions

1. Why do drugs for 3rd world diseases look like this?
2. If these molecules have higher risk, how do we manage these risks?
3. Are there any lessons from 3rd world disease drugs?
4. Have we become too dogmatic in how we judge molecules?

1) Why do drugs for 3rd world diseases look like this?

- Age of drugs
- Historical (natural) source of drugs
- Nature of the beast:
  - Permeability barriers (waxy cell walls, intracellular location)
- Activatable "warheads" for maximal activity
  - Nitro groups, endoperoxides, acylhydrazides
  - Hit multiple targets; minimize resistance, kill quickly
  - Use parasitic machinery for selective activation
- Non specific mechanisms
  - Membrane disruption
  - Cellular accumulation

Proposed Mechanism of Action of Some Commonly Used Third-World Disease Drugs

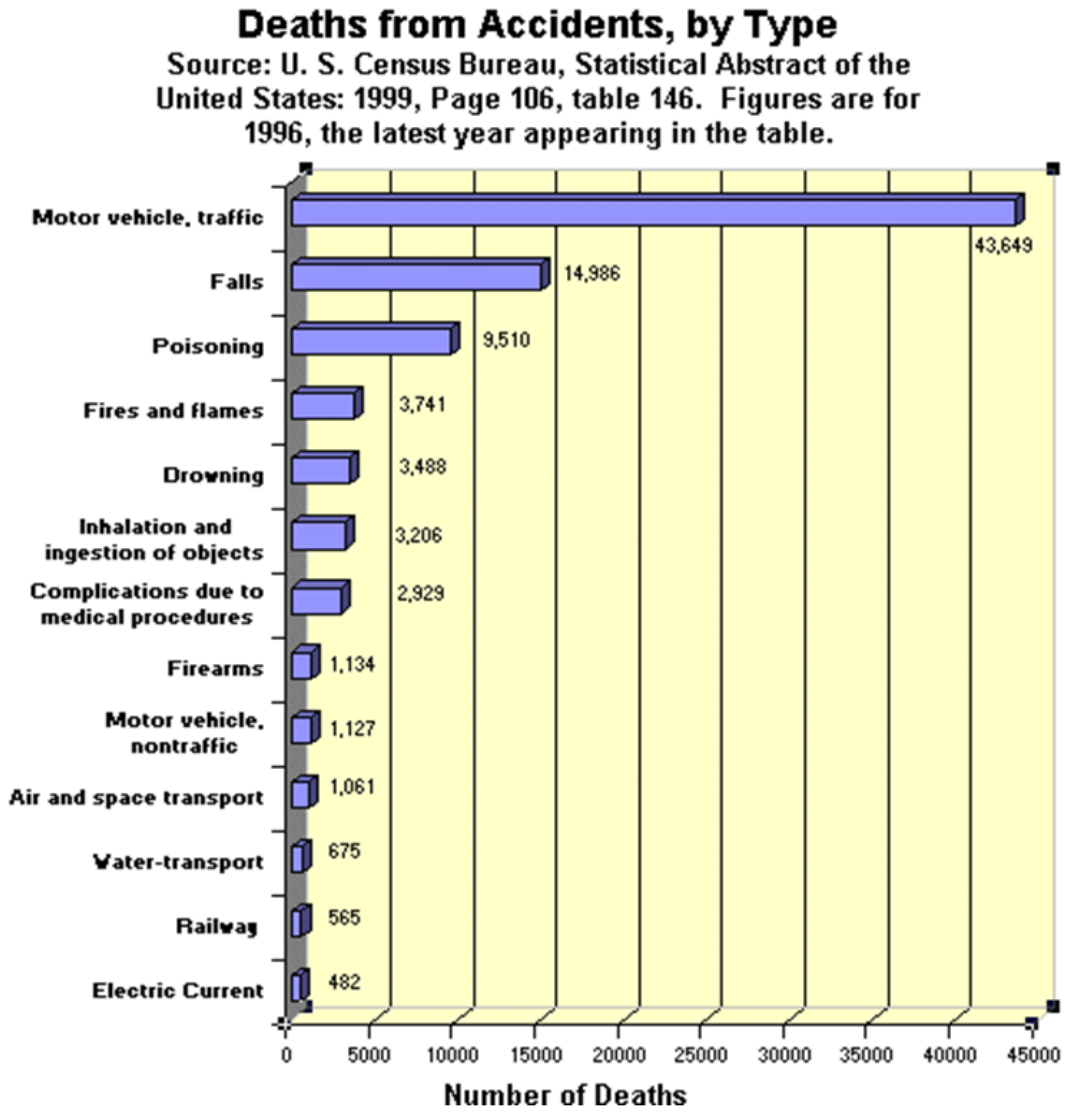
Amikacin	inhibits protein synthesis by binding to the 30S ribosomal unit
Amphotericin B	forming a transmembrane channel that leads to monovalent ion leakage
Artemesinin	endoperoxide activated to reactive intermediate(s)
Atovaquone	mitochondrial electron transport, ATP and pyrimidine biosynthesis.
Capreomycin	inhibits protein synthesis by binding to the 70S ribosomal unit
Clofazimine	binds to the guanine bases of bacterial DNA
Isoniazid	activated by catalase-peroxidase enzyme (KatG) to reactive intermediate
Ivermectin	binds and activates glutamate-gated chloride channels
Lumefantrine	not well defined; perhaps inhibits the formation of ß-hematin
Melarsoprol	disruption of energy generation due to the high affinity for sulfhydryl groups
Nifurtimox	bioreductive activation of nitro group
Nitazoxanide	Bio-reductive activation of nitro group
Proguanil	inhibits dihydrofolate reductase (prodrug), perhaps other targets
Rifampin	inhibit mycobacterial transcription by targeting DNA-dep. RNA polymerase

= non-specific/"warhead" mechanism of action

2) If these molecules have higher risk, how do we manage these risks?

- Utilize modern state-of-the-art risk-management tools and approaches
  - Computational
  - In vitro
  - In vivo
- Develop new risk-management tools and methods
- Adapt a portfolio approach to the discovery pipeline
- Make data-driven decisions regarding series, compounds

Without Data, Risk Assessment can be Subjective



"Yes, I used to trade stocks, but I found it too risky."

3) Are there any lessons from 3rd world disease drugs?

- Don't be too proscriptive/dogmatic in assessing risks- keep an open mind.
- We have explored much less chemical diversity than we think we have.
- We need new chemistry to access addition chemical diversity.
- Our risk assessment tools are still inadequate
- We still have much to learn from nature!

4) Have we become too dogmatic in how we judge molecules?

Yes (we tend to be):

- We need to remain open-minded about the physiochemical space and chemotypes we are willing to explore
- We have developed “rules” rather than “guidelines”
- We have under-estimated the risks of not taking risks

- We still aren’t really able to distinguish good from bad/ugly.

Question: How do you define an ugly molecule?

Answer: An ugly molecule should be defined by what it does, not by how it looks

The End

Drugs for 3rd World Diseases: The Good, the Bad, and the Ugly

Over the last 15 years numerous empirically-derived rules, guidelines, and tools based on retrospective analyses have been developed to enable medicinal chemists to better understand and more effectively manage drug development risks associated with a drug candidate's chemical structure and physiochemical properties. These analyses have led to a greater consensus within the drug development community regarding acceptable physiochemical properties and structural motifs for drugs. However, analysis of current drugs used for the treatment of 3rd world diseases, most of which are safe and efficacious, and many of which have been dosed in millions of patients, reveals a multitude of "forbidden" functionalities (structural alerts) and "unacceptable" properties, including endoperoxides, nitro-aromatics, and large macrocyclic ring systems which fall well outside the canonical "rule of five" boundaries. This raises a number of fundamental questions, including does drug discovery for 3rd world diseases require different thinking and risk-tolerance regarding molecular properties and chemical functionalities from 1st world disease drug discovery? If so, how can we further understand these differences and capitalize on this knowledge to better develop and risk-manage the 3rd world drug discovery portfolio?