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Charting the unknown – Novel targets and oral bioavailability bRo5

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Journal of Medicinal Chemistry

Perspective

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Macrocyclic Drugs and Clinical Candidates: What Can Medicinal Chemists Learn from Their Properties?

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Chemistry & Biology

Review

Oral Druggable Space beyond the Rule of 5: Insights from Drugs and Clinical Candidates

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How Beyond Rule of 5 Drugs and Clinical Candidates Bind to Their Targets

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Understanding macrocycle cell permeability
Over, B., Matsson, P., Tyrchan, C., Artursson, P., Doak, B.C., Foley, M., Hilgendorf, C., Johnston, S.E., Lee, M.D., Lewis, R.J., McCarren, P., Muncipinto, G., Perry, M., Duvall, J.R., Kihlberg, J.
Nature Chemical Biology, *under revision*

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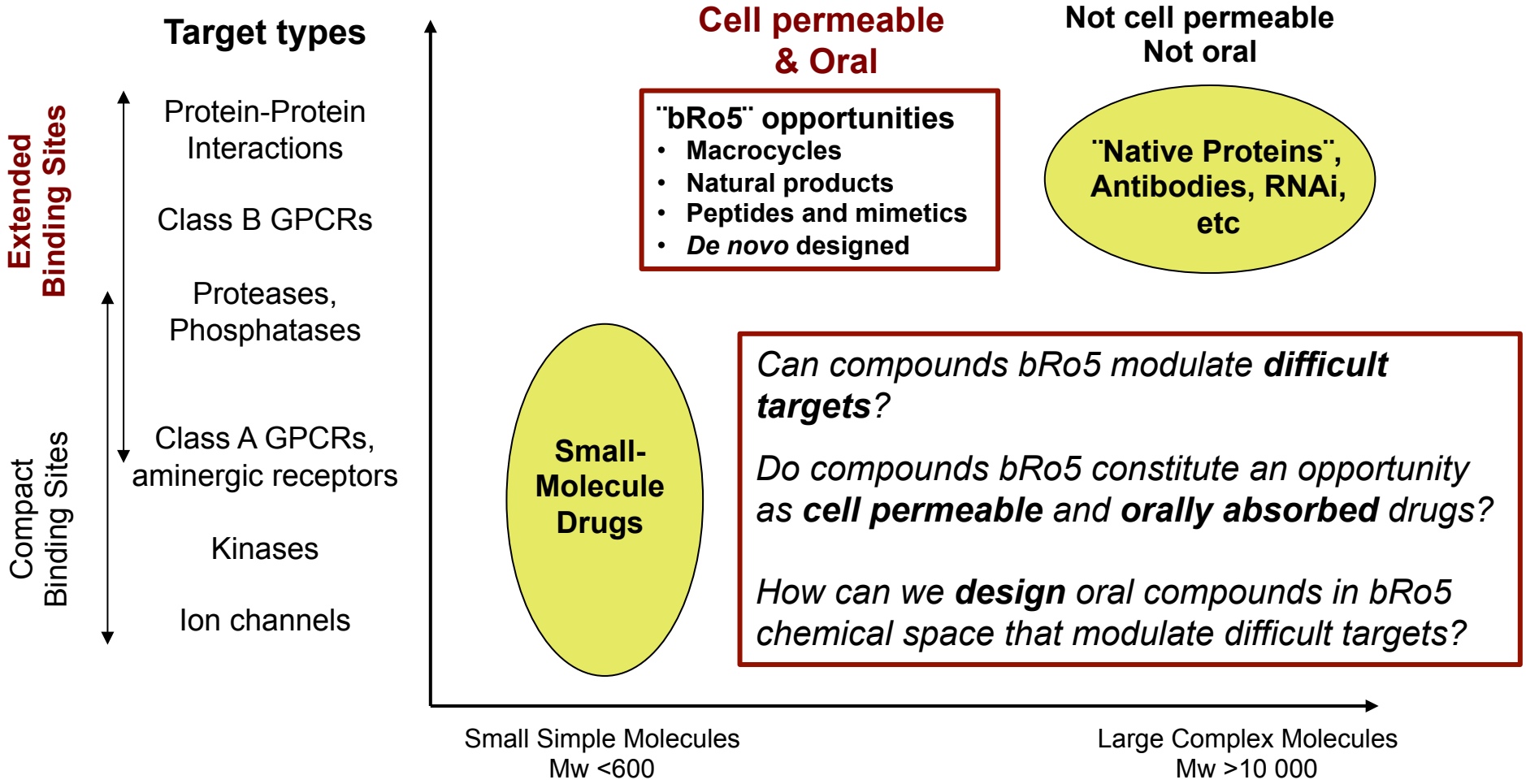
Opportunities for small molecule drugs in chemical space beyond ¨the rule of 5¨



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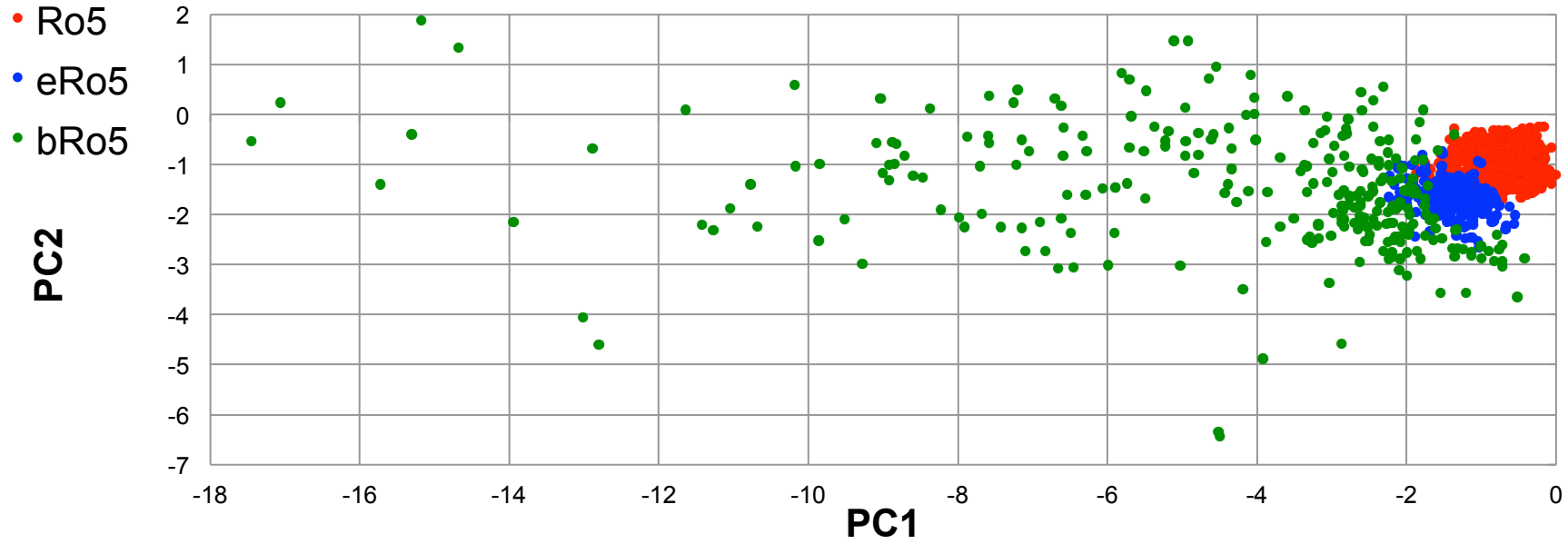
The Drugs and Clinical Candidates Datasets - Properties retreived from literature and calculated

	Ro5 (N=579)	eRo5 (N=195)	bRo5 (N=280)
MW	≤500	500-700	500-3000
cLogP	0-5	0-7.5	<0 or >7.5
HBD	≤5	≤5	>5
HBA	≤10	≤10	>10
PSA (Å^2)		≤200	>200
NRotB		≤20	>20

Ro5: All properties within guidelines

eRo5: At least one property outside of Ro5 space, but all within outer limits of eRo5 space

bRo5: At least one property outside of eRo5 space



Doak, et al., *Chemistry & Biology,* **2014**, *21*, 1115; *J. Med. Chem.*, **2016** DOI: 10.1021/acs.jmedchem.5b01286

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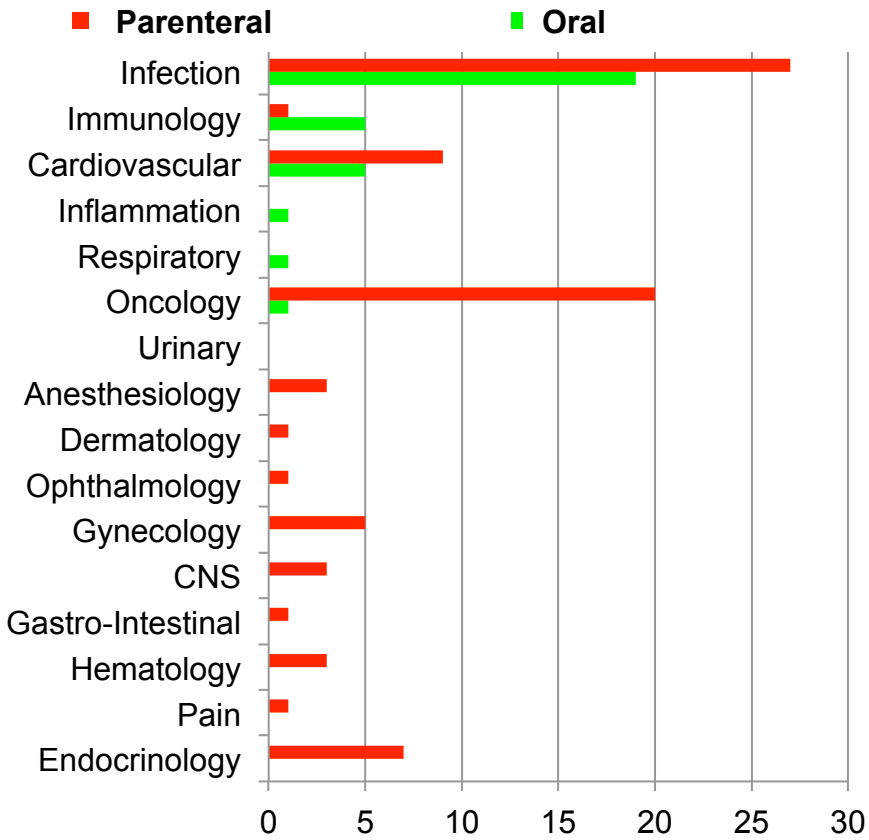
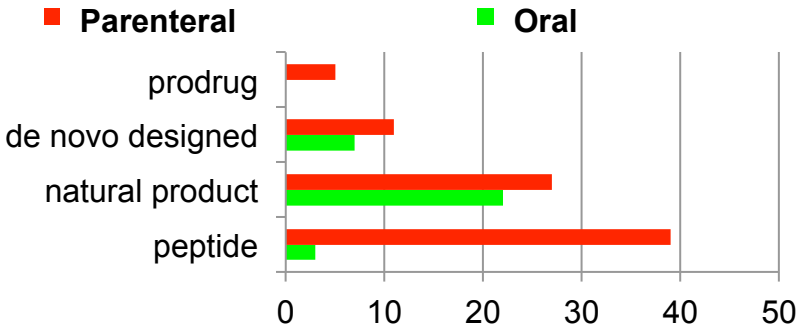
Drugs bRo5 – Indications, Route of Administration and Chemical Classes

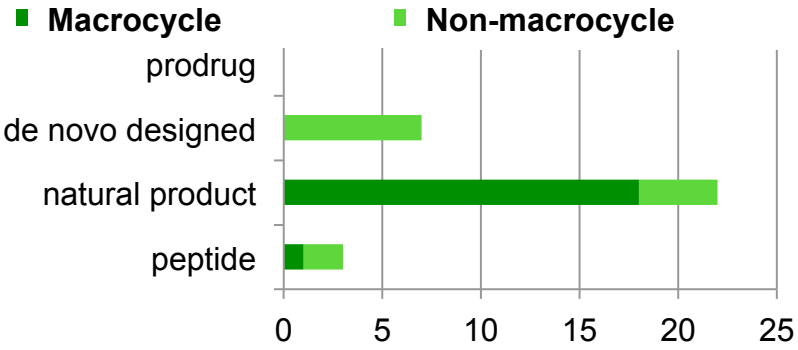
114 approved drugs in bRo5 space - 32 (28 %) administered orally



Chemical class – All drugs



Chemical class – <u>Oral</u> drugs



- **Infection (40%), oncology (18%) and CV (12%) dominate**
- **Most orals for infection**

- **Natural products and peptides dominate**
- **Orals are macrocyclic natural products**

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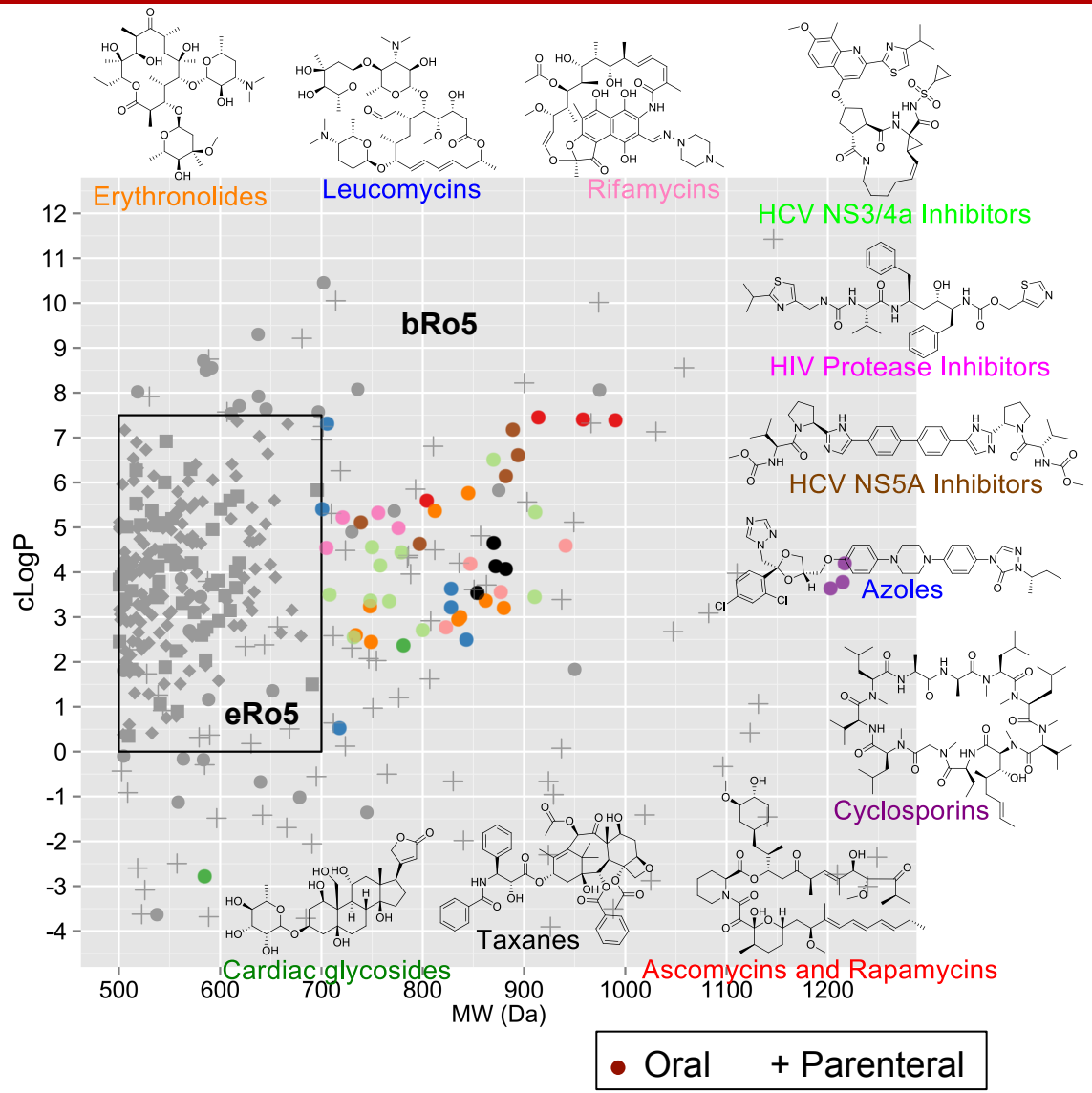
Why care about bRo5 drugs & clinical candidates?

- Because they treat life-threatening disease!



Antibacterials
- Erythronolides
- Leucomycins
- Rifamycins

Antivirals
- HIV protease inhibitors
- HCV NS3/4A protease inhibitors
- HCV NS5A inhibitors

Antifungals
- Azoles

Immunosuppressants
- Ascomycins and Rapamycins
- Cyclosporins

Anticancer agents
- Taxanes

Heart stimulators
- Cardiac glycosides

bRo5 orals

Macrocycle	32
Non-macrocycle	53
Natural product	34
De novo designed	29
Peptide	16
Prodrug	6

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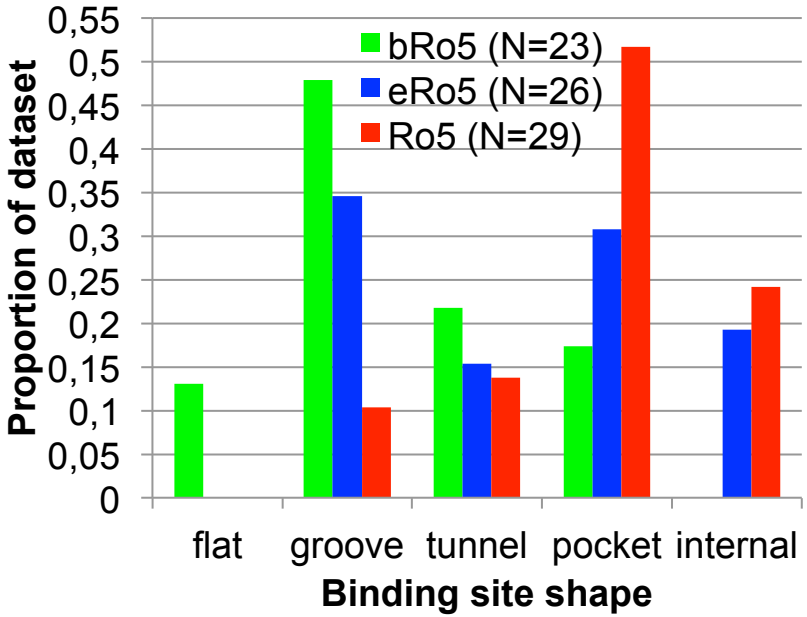
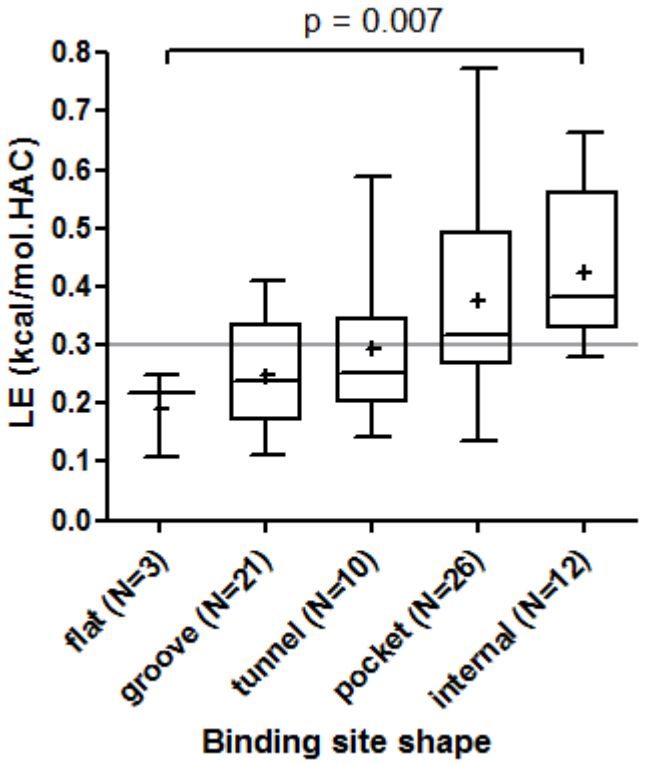
bRo5 drugs and clinical candidates bind to sites that have different shapes than Ro5 drugs

Flat and groove shaped binding sites can be modulated by bRo5 drugs



- Strucures of drug-target complexes determined by X-ray crystallography
- Only drug targets included
- Redundant compounds binding to same target excluded (e.g. only one member of erythronolides included)

LE depends on binding site shape



Keep in mind when working on a ¨difficult¨ target

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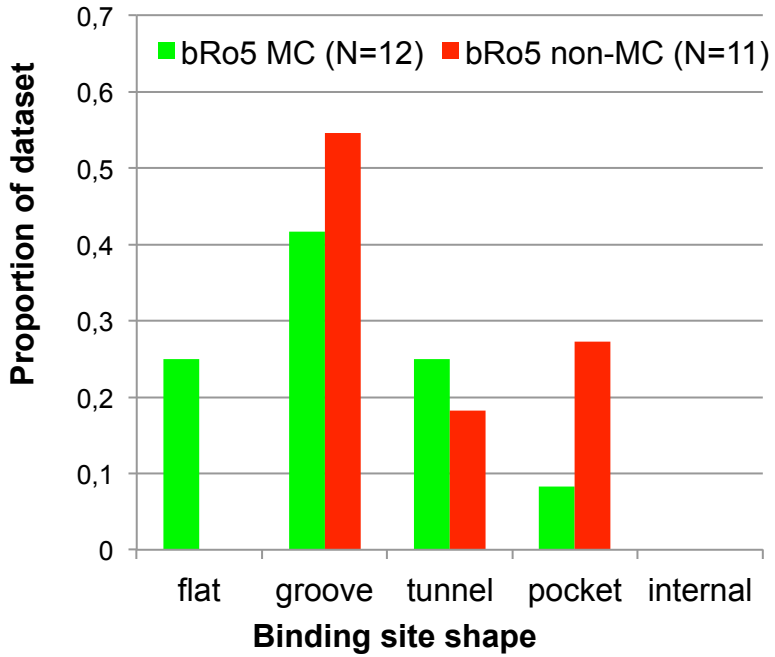
Binding site preferences of macrocyclic and non-macrocyclic drugs bRo5

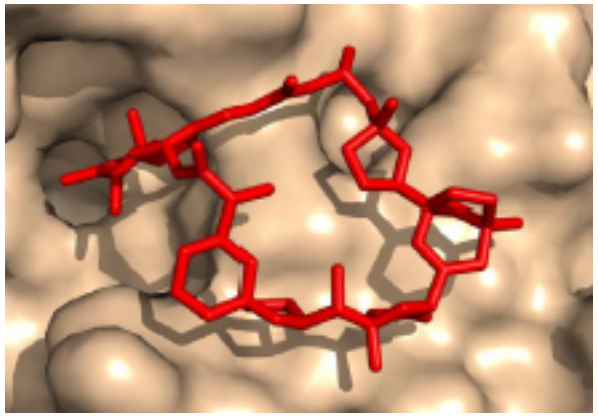
Macrocycles are better ligands for flat sites than non-macrocycles



Explanation for why macrocycles are enriched bRo5

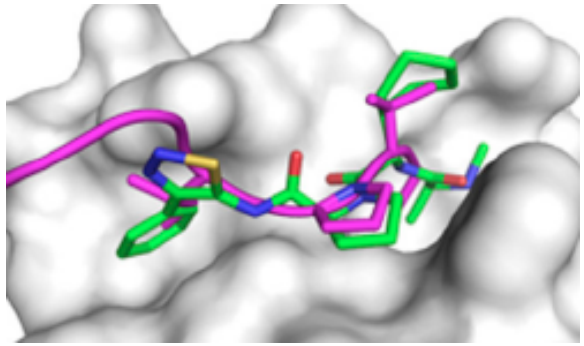
- **In addition to influence on <u>permeability</u>**

Macrocyclic natural products bind face-on to flat binding sites



Villar, *Nature Chem. Biol.*, **2014**, *10*, 723

De novo designed inhibitors of PPIs bind to grooves or pockets



Arkin, *Chemistry & Biology,* **2014**, *21*, 1102

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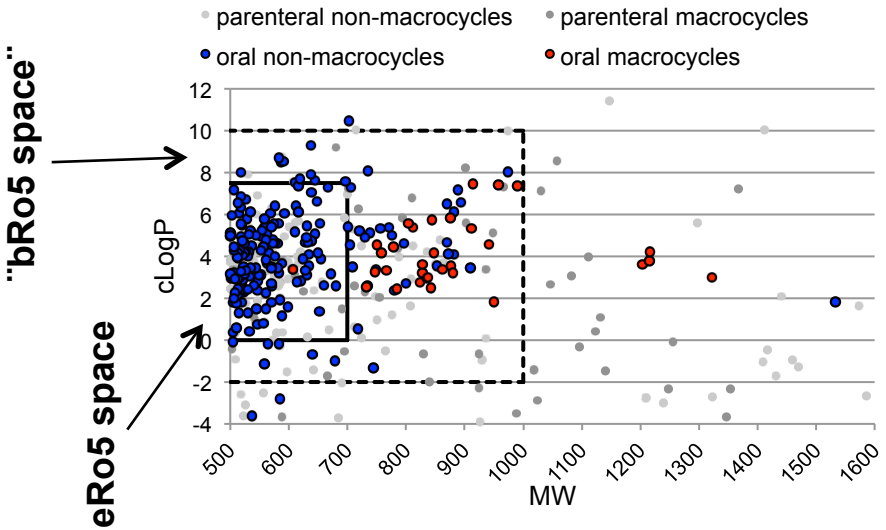
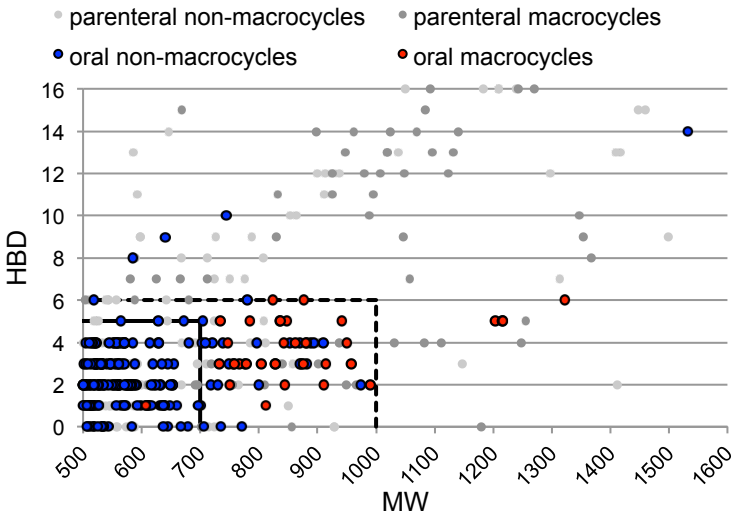
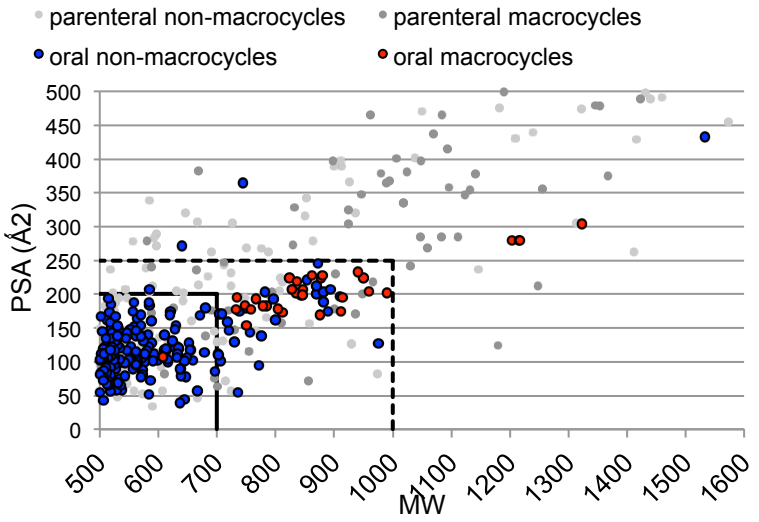
Outer limits of oral druggable space bRo5 -

Learnings from drugs and clinical candidates with MW>500







Current limits of oral chemical space

- MW ≤1000 Da
- -2≤ cLogP ≤10
- tPSA ≤250 Å^2
- HBD ≤6
- HBA ≤15
- NRotB ≤20

Opportunity bRo5

Macrocycles are enriched bRo5

Doak, et al., *Chemistry & Biology,* **2014**, *21*, 1115

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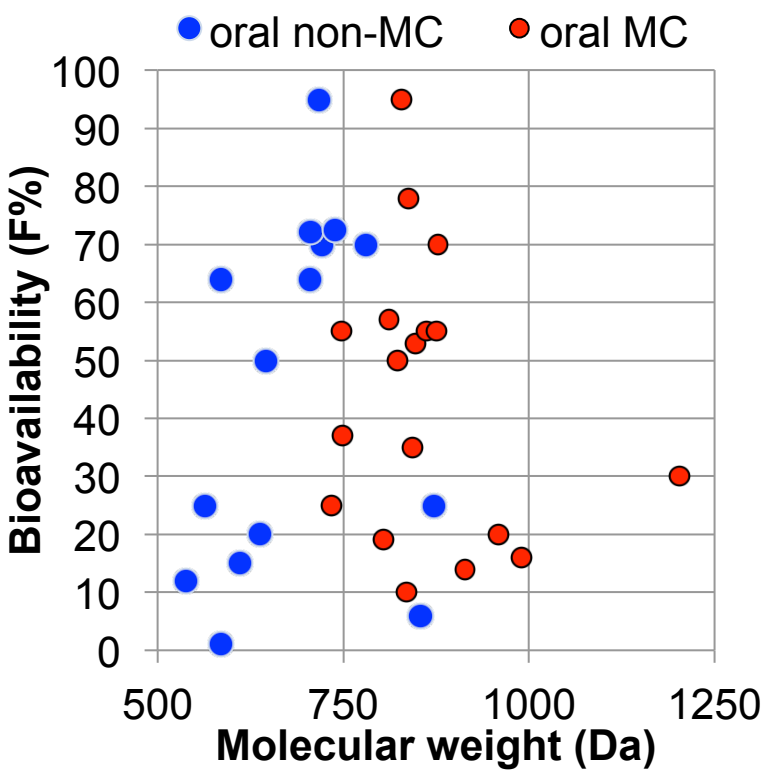
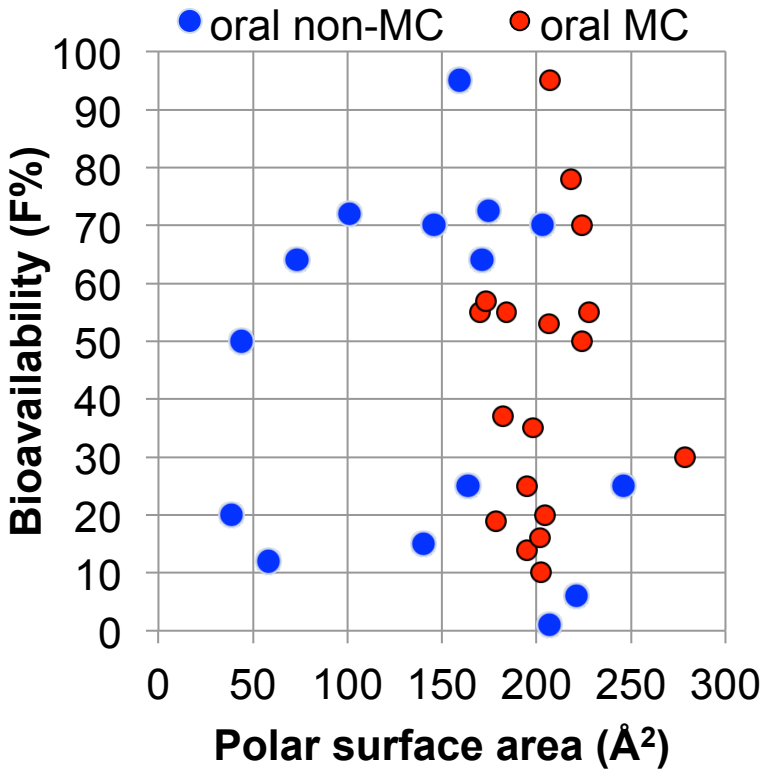
eRo5 and bRo5 drugs have satisfactory bioavailability

It is not correlated to physicochemical properties



No correlation to MW, but possibly lower at high MW (=high CLogP)



No correlation to PSA, nor to HBD (data not shown)

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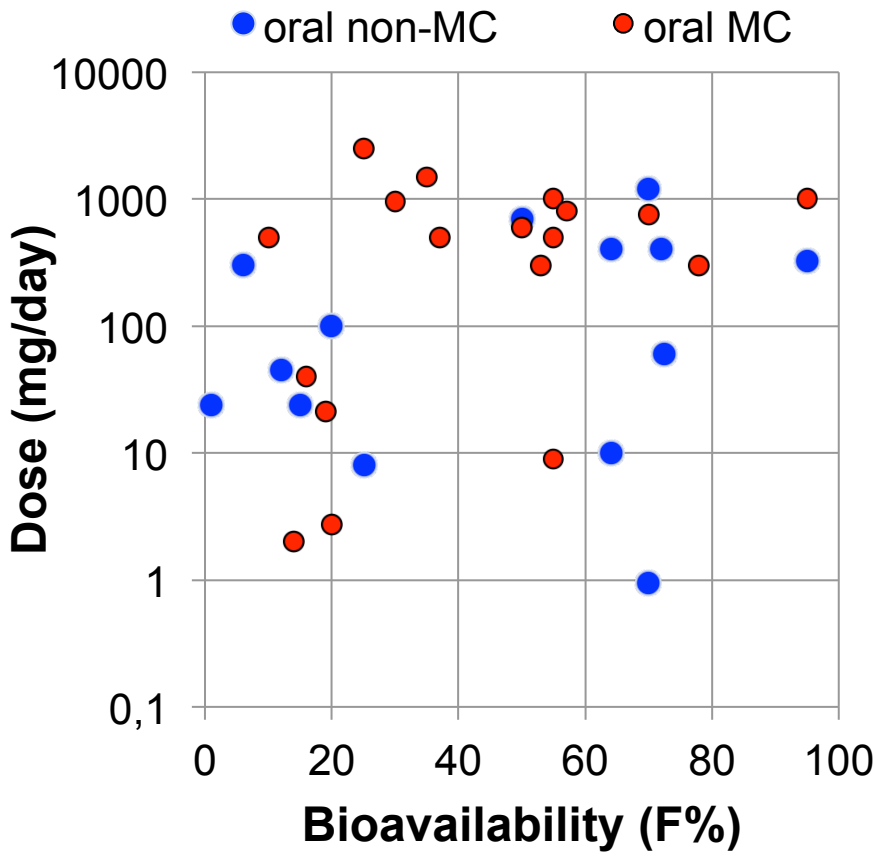
Doses are often high for eRo5 and bRo5 drugs



High doses are not used to compensate for very low bioavailabilities

Oral and parenteral drugs have similar doses

- mean/median:
  - orals: 423/300 mg
  - parenterals: 444/61 mg

High doses are connected to use in infectious disease

- mean/median
  - orals: 689/500 mg
  - parenterals: 1145/600 mg

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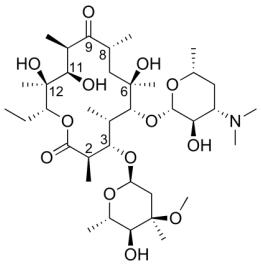
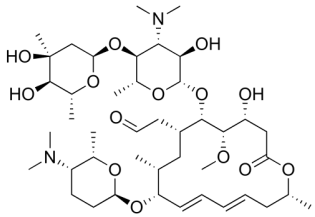
All major classes of oral macrocyclic drugs and clinical candidates bRo5 show efflux

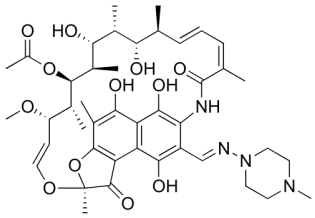
Antibacterials



Erythromycin
2500 mg/day

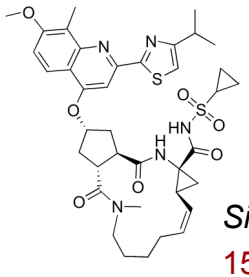


Spiramycin
1500 mg/day

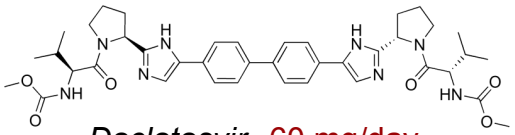


Rifampicin
600 mg/day

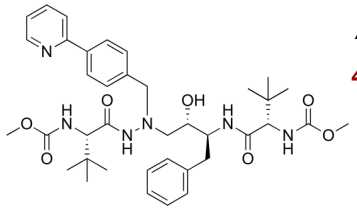
Antivirals



Simeprevir
150 mg/day

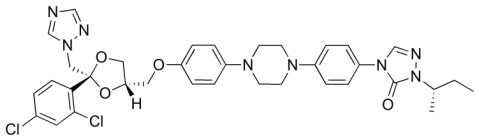


Daclatasvir 60 mg/day



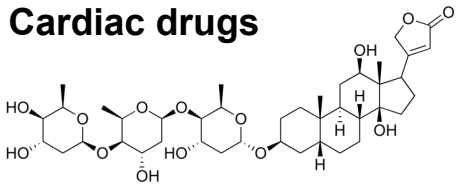
Atazanavir
400 mg/day

Antifungal



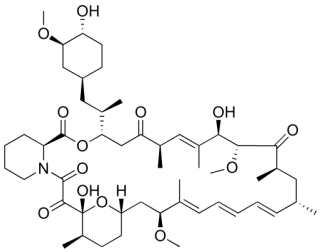
Itraconazole 400 mg/day

Cardiac drugs

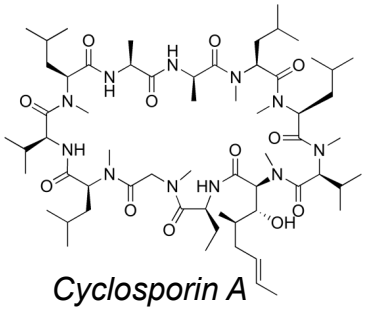


Digoxin 0.95 mg/day

Immunosuppressants



Sirolimus 2 mg/day



Cyclosporin A
950 mg/day

All classes associated with efflux
- Pgp and other transporters

Medium -> high doses will saturate efflux transporters in intestine
–> Bioavailability is sufficient if permeability is moderate to high

Even low doses may overcome efflux in the intestine

CNS penetration is likely to be low

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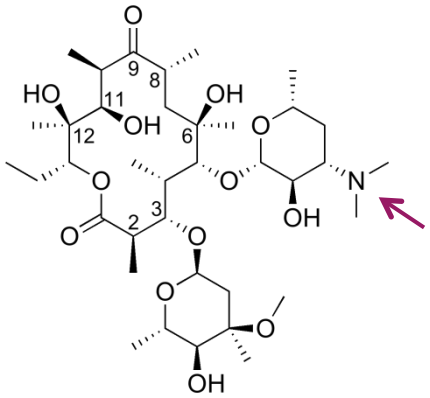
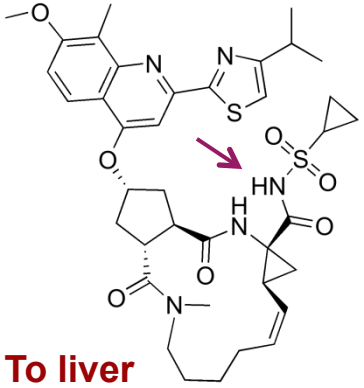
Transporters may improve distribution to target organs

Erythronolides (N=9)



To lungs & phagocytic cells

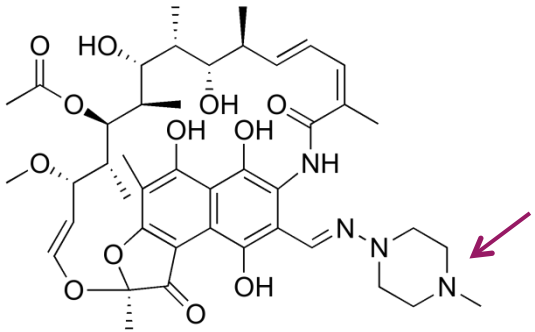
HCV NS3/4A inhibitors (N=11)



To liver

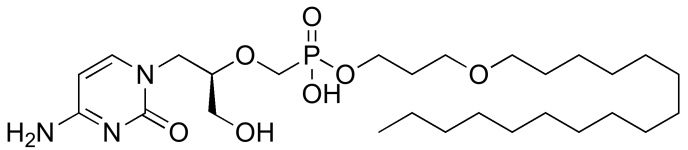
- Lung accumulation due to Pgp
- Accumulation in lysosomes of phagocytic cells because of charge
- Liver accumulation due to OATPs

Rifamycins (N=4)



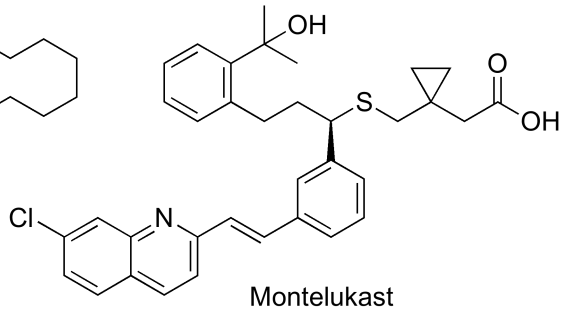
To lungs & phagocytic cells

Little *data* for active uptake from intestine



Brincidofovir (PIII)

Antiviral, proposed to be absorbed through endogenous fatty acid uptake pathways



Montelukast

Conflicting data

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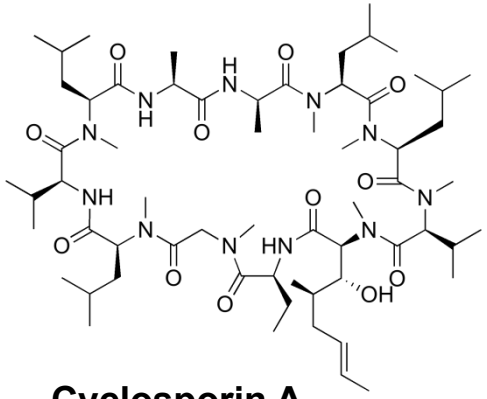
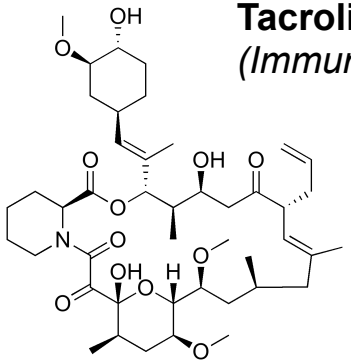
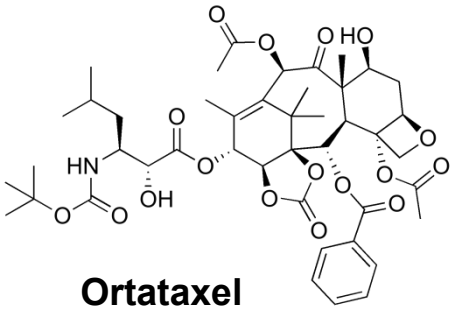
Improving bioavailability – By use of formulations



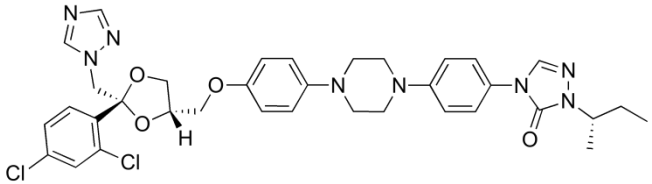
Cyclosporin A
(Immunosupp.)



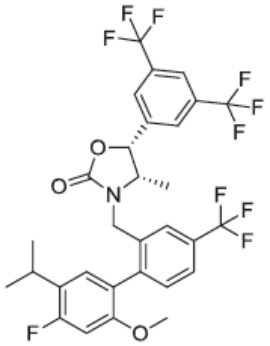
Tacrolimus
(Immunosupp.)



Ortataxel
(Cancer)



Itraconazole
(Antfungal)



Anacetrapib
(Atherosclerosis, PIII)

Formulations increase bioavailability and reduce variation

- Cyclosporin A: 5 -> 60%
- Tacrolimus: -> 19%
- Ortataxel: -> 25%
- Itraconazole: -> 72%
- Anacetrapib: -> 20%

Often lipid based

But, difficult to predict efflux, transporter-mediated uptake and formulation effects => How about passive permeability??

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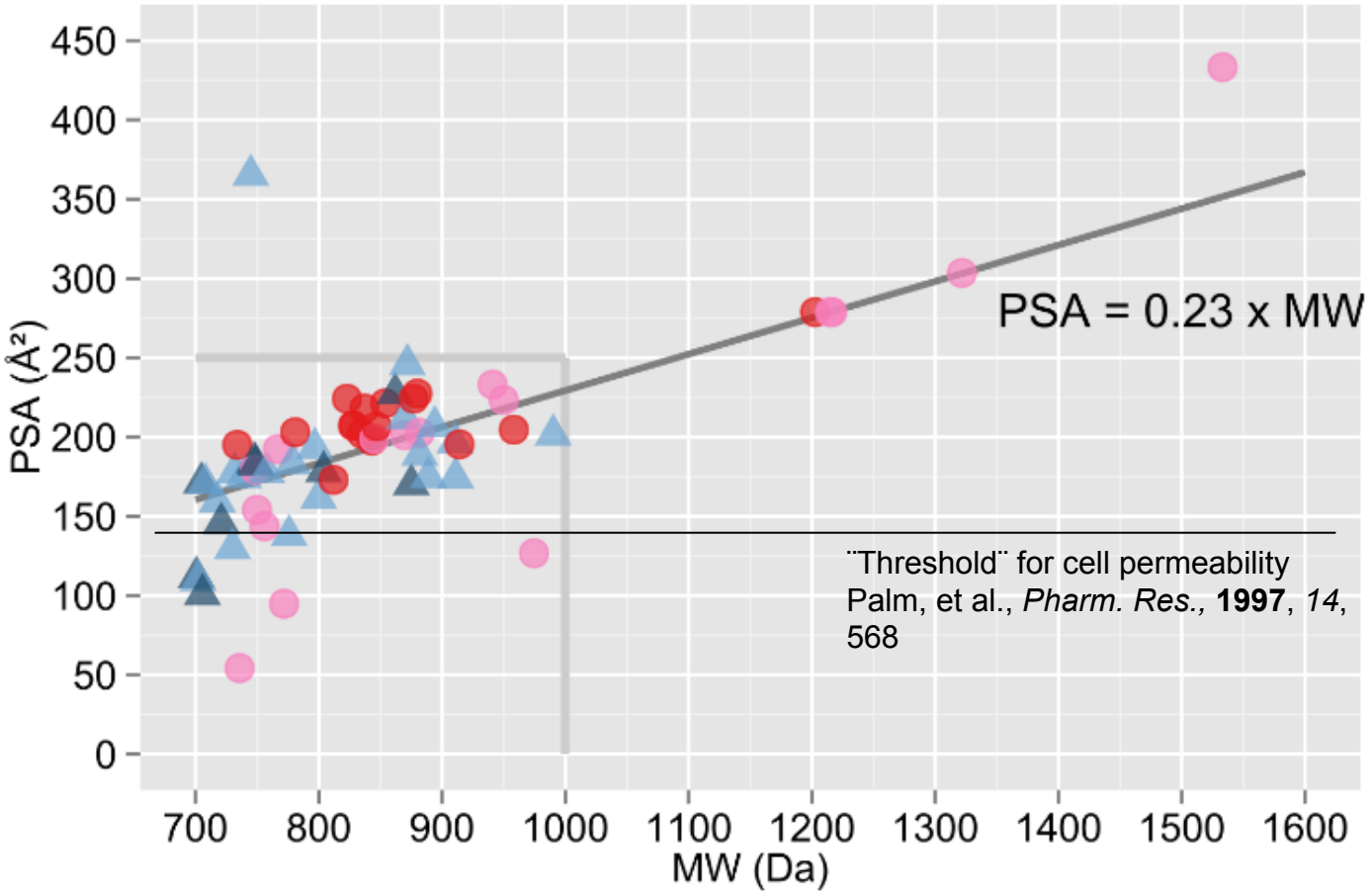
Understanding cell permeability and oral absorption

bRo5 - Progress towards predictions



Orals in bRo5 space

Classification

- MC
- non-MC

Development

- MC APP
- MC CLIN
- non-MC APP
- non-MC CLIN

- TPSA of orals is too high in bRo5 space

- How is cell permeability achieved at PSA >140 Å²?

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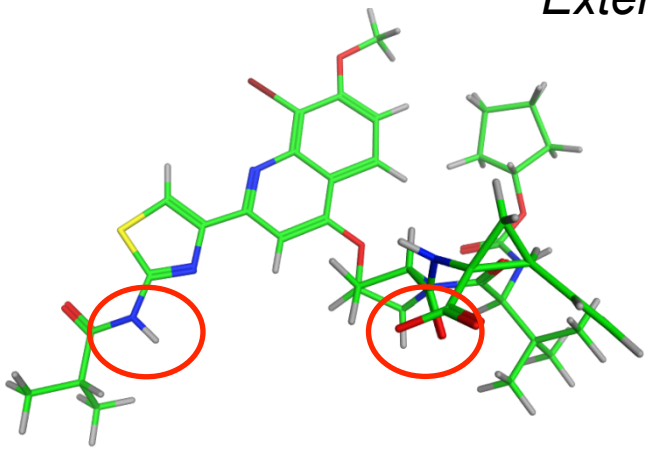
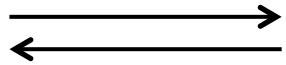
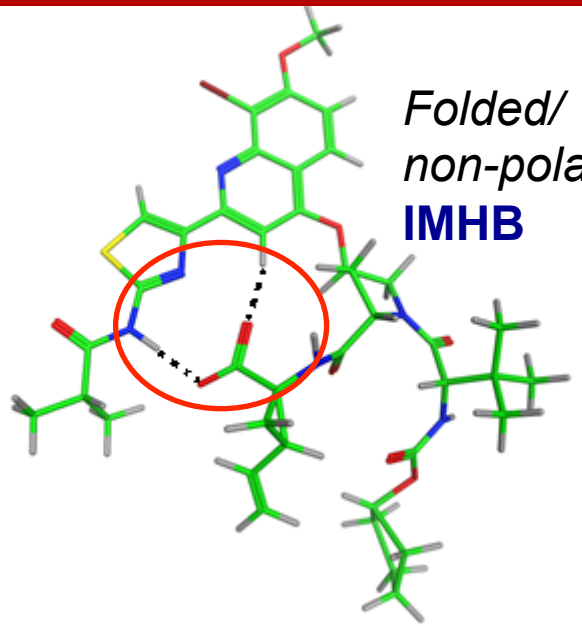
Impact of conformational flexibility on 3D PSA - Faldaprevir and Telithromycin

Faldaprevir

Extended/polar





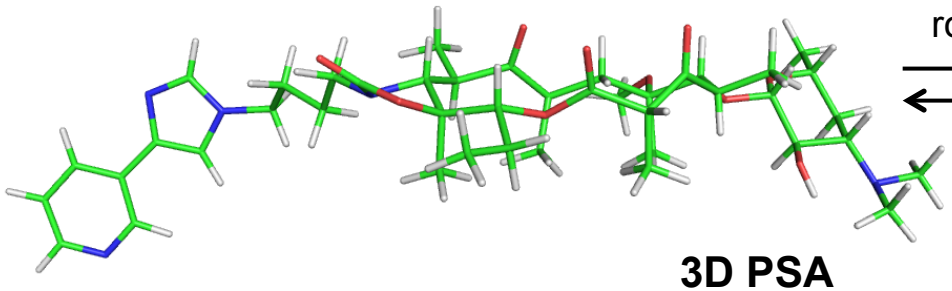


Folded/ non-polar **IMHB**

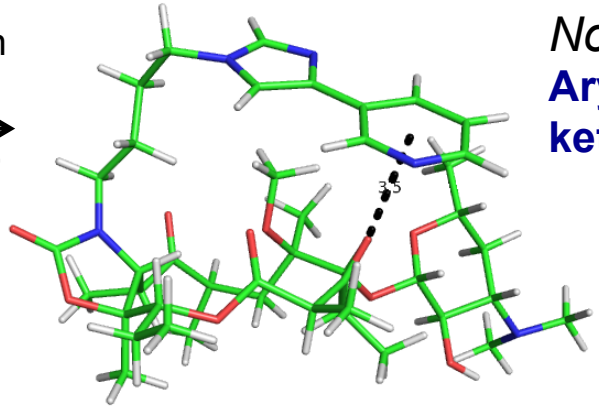
3D PSA
CDK: 212 -> 138 Å^2
Spartan: 148 -> 131 Å

Telithromycin

Polar



Side chain rotation



Non-polar **Aryl π – ketone LP**

3D PSA
CDK: 200 -> 129 Å^2
Spartan: 127 -> 96 Å^2

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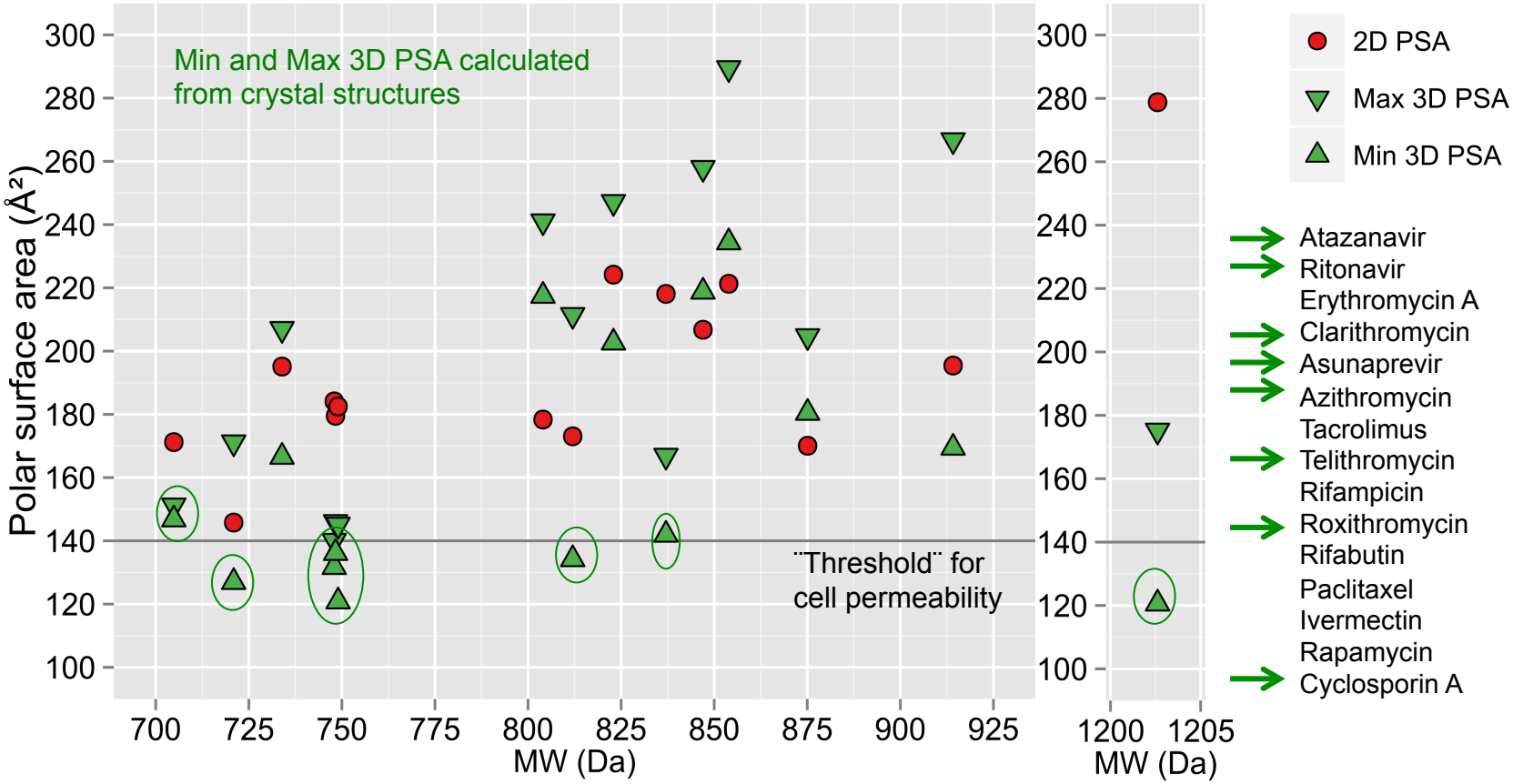
Conformational flexibility - May provide high solubility and cell permeability



- Max 3D PSA adopted in water **=>aqueous solubility**
- Min 3D PSA adopted in membrane **=>cell permeability**

Min 3D PSA reduced due to

- Shielding by bulky hydrophobic side chains
- Intramolecular hydrogen bonding
- Dipole-dipole interactions (aryl π – ketone LP)

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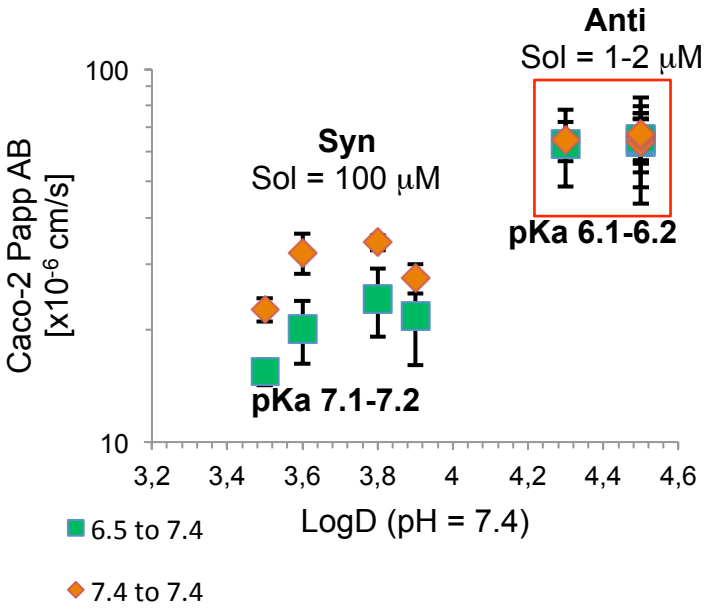
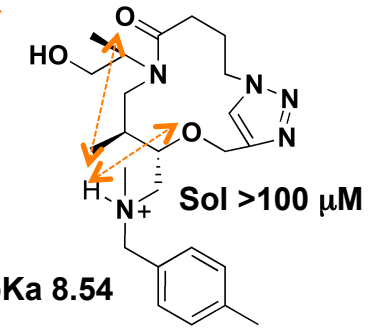
Dynamic intramolecular hydrogen bonding allows high solubility and cell permeability

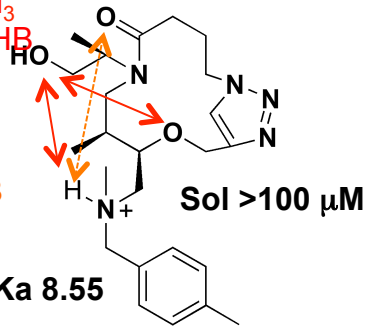


DMSO & $CDCl_3$ 1 IMHB

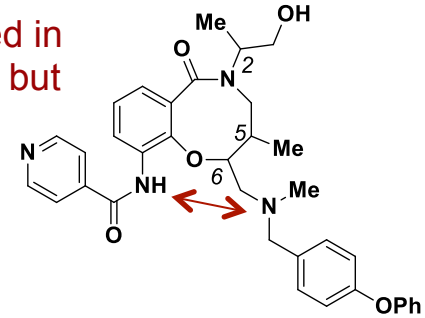


$CDCl_3$ 2 IMHB

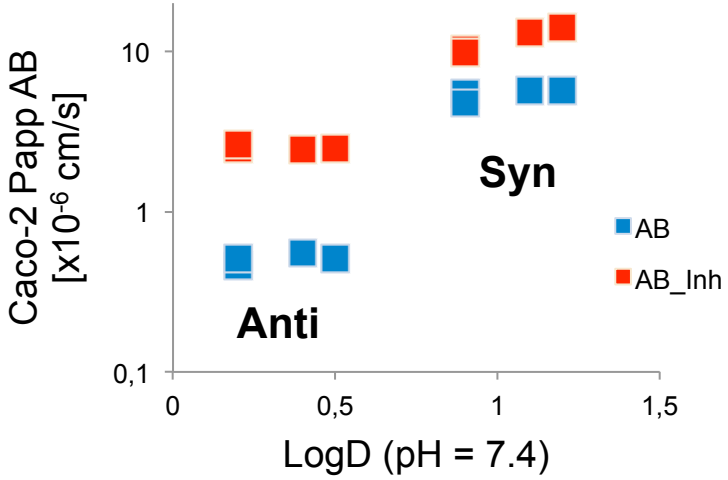
DMSO, 1 IMHB



Static IMHB formed in C5,C6-***trans***-form, but not in cis-form – **Independent of environment**



Over, *J. Med. Chem.*, **2014**, *57*, 2746



Dynamic IMHB network formed in ***syn***-form, but not in anti-form – ***Syn* is highly soluble and permeable**

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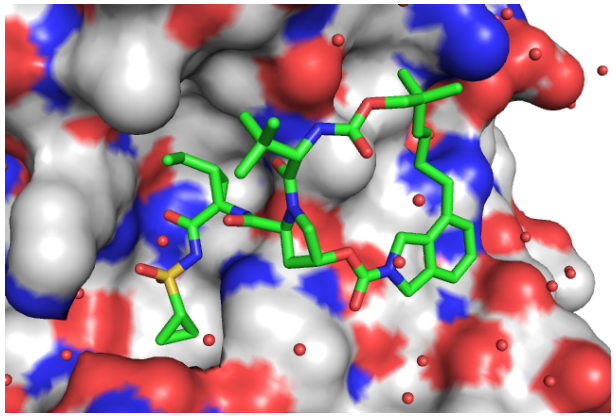
Key Findings and Guidelines for Design – Cell permeable and orally absorbed bRo5

Targets that have difficult binding sites can be modulated

- Flat and groove-shaped sites
- ***But***, allow for low LE

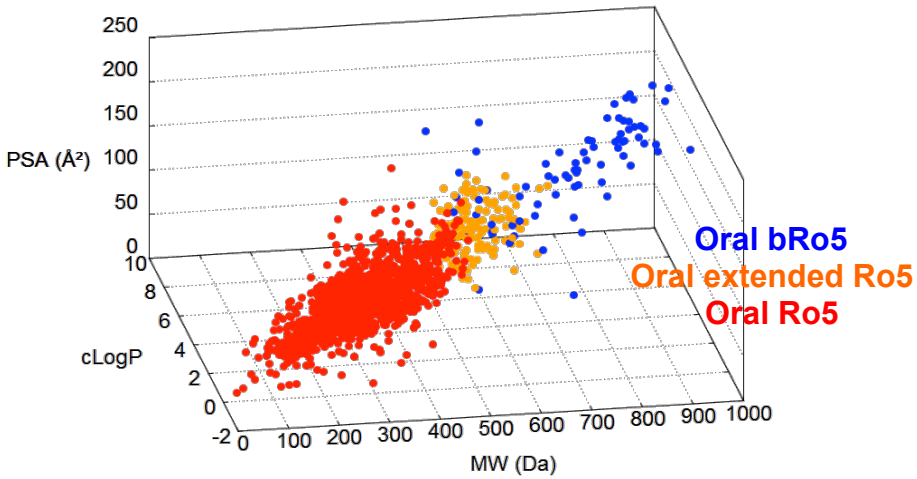


QSPR models and conformational analysis may predict cell permeability

- Consider conformational ensembles
- Consider IMHB and shielding of polarity

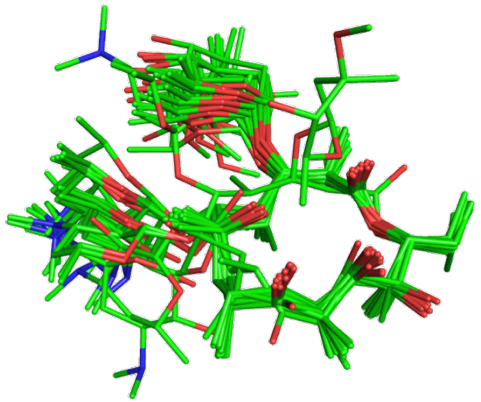
Oral absorption can be obtained far bRo5

- Mw ≤1000, cLogP ≤10, PSA ≤250 Å²
- ***But***, HBD limited *to ≤6*
- Efflux can be managed, but needs monitoring



Not too flexible, nor too rigid

- Soluble and permeable
- Target binding
- ***Incorporate in design?***



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