The Effect of Excipients on Intestinal Drug Transporters

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UCSF

USP-FDA Workshop: Critical Importance of Excipients

2017

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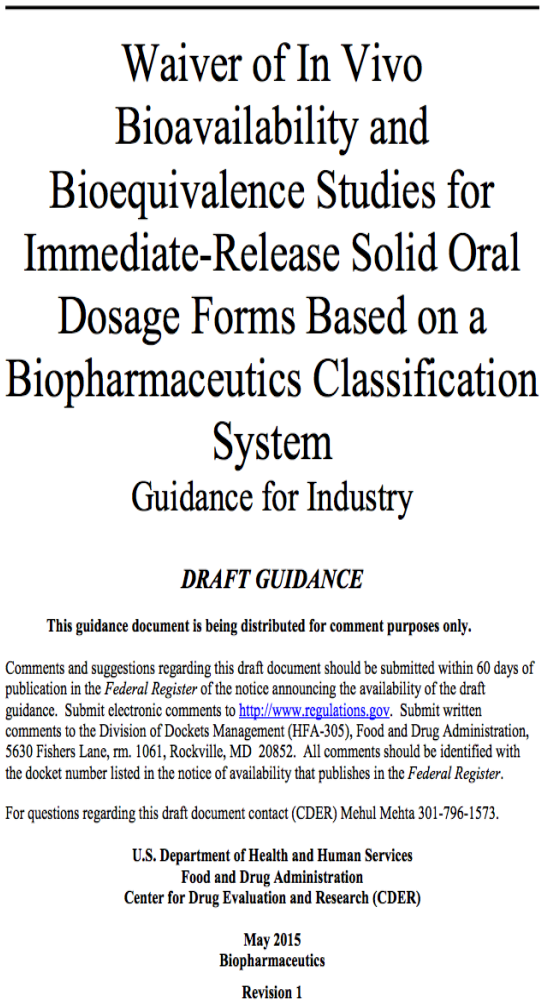
Biopharmaceutical Classification System Class 3 Biowaivers



Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Mehul Mehta 301-796-1573.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2015
Biopharmaceutics

Revision 1

BCS Class 3 Drugs

Low Permeability/
High Solubility Drugs

e.g., cimetidine, metformin, acyclovir, fexofenadine

Influx Transporters

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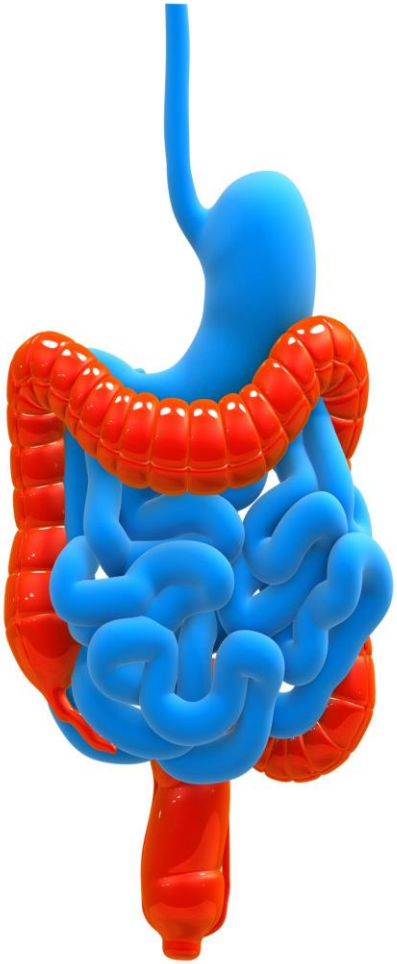
Intestinal Drug Transporters



ABC Superfamily

- P-glycoprotein (ABCB1)
- BCRP (ABCG2)

Efflux

SLC Superfamily (Solute Carrier Superfamily)

- PEPT1 (SLC15A1)
- OATP2B1 (SLCO2B1)
- THTR2 (SLC19A3)

Influx

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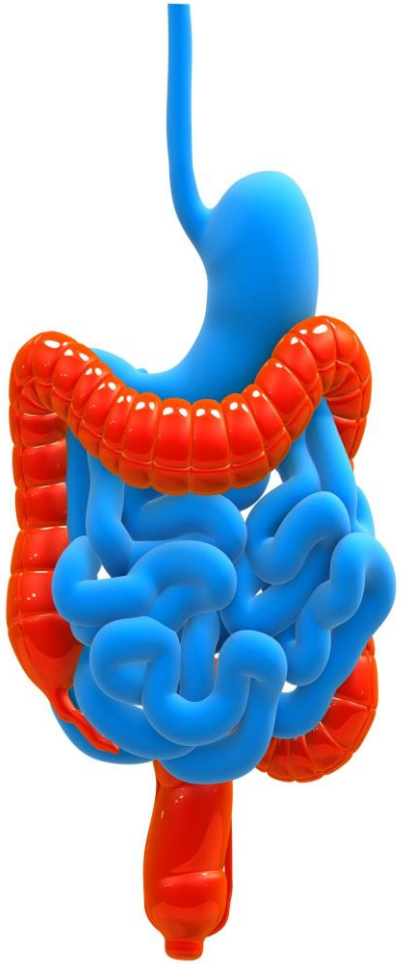
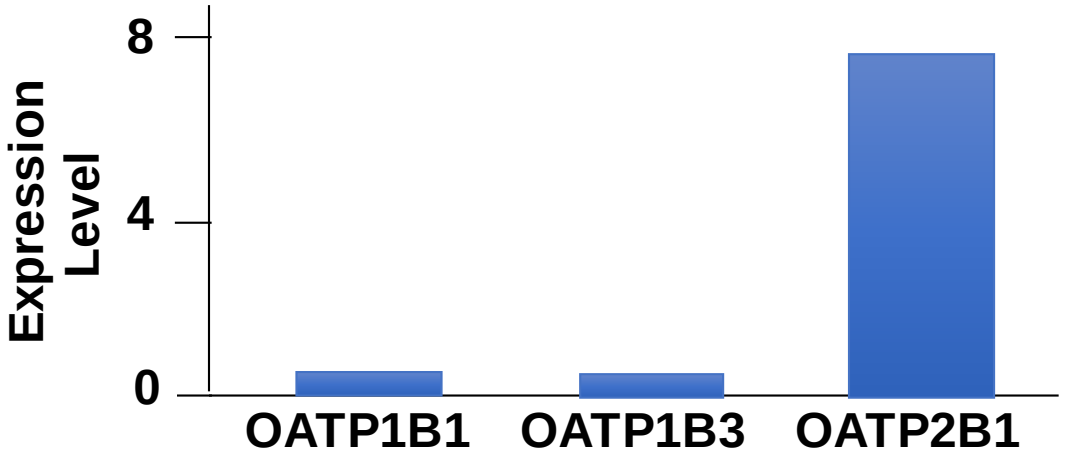
Organic Anion Transporting Polypeptide, OATP2B1- High Expression In Intestine





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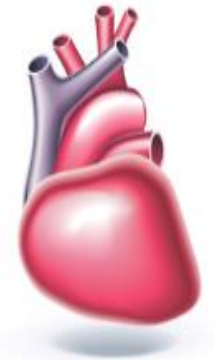
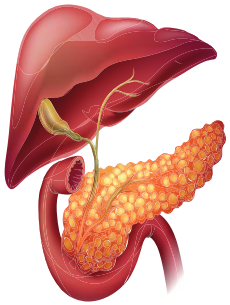
OATP2B1 Interacts with Structurally Diverse Drugs

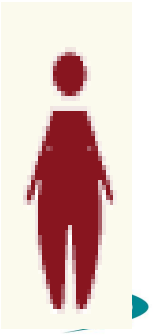
- Cardiovascular Drugs
  - Statins (fluvastatin, rosuvastatin)
  - Beta-adrenergic blocking agents (talinolol)



- Hormones (estrone-3-sulfate)



- Anti-diabetic agents (glyburide)



- Antihistamines (**fexofenadine**)

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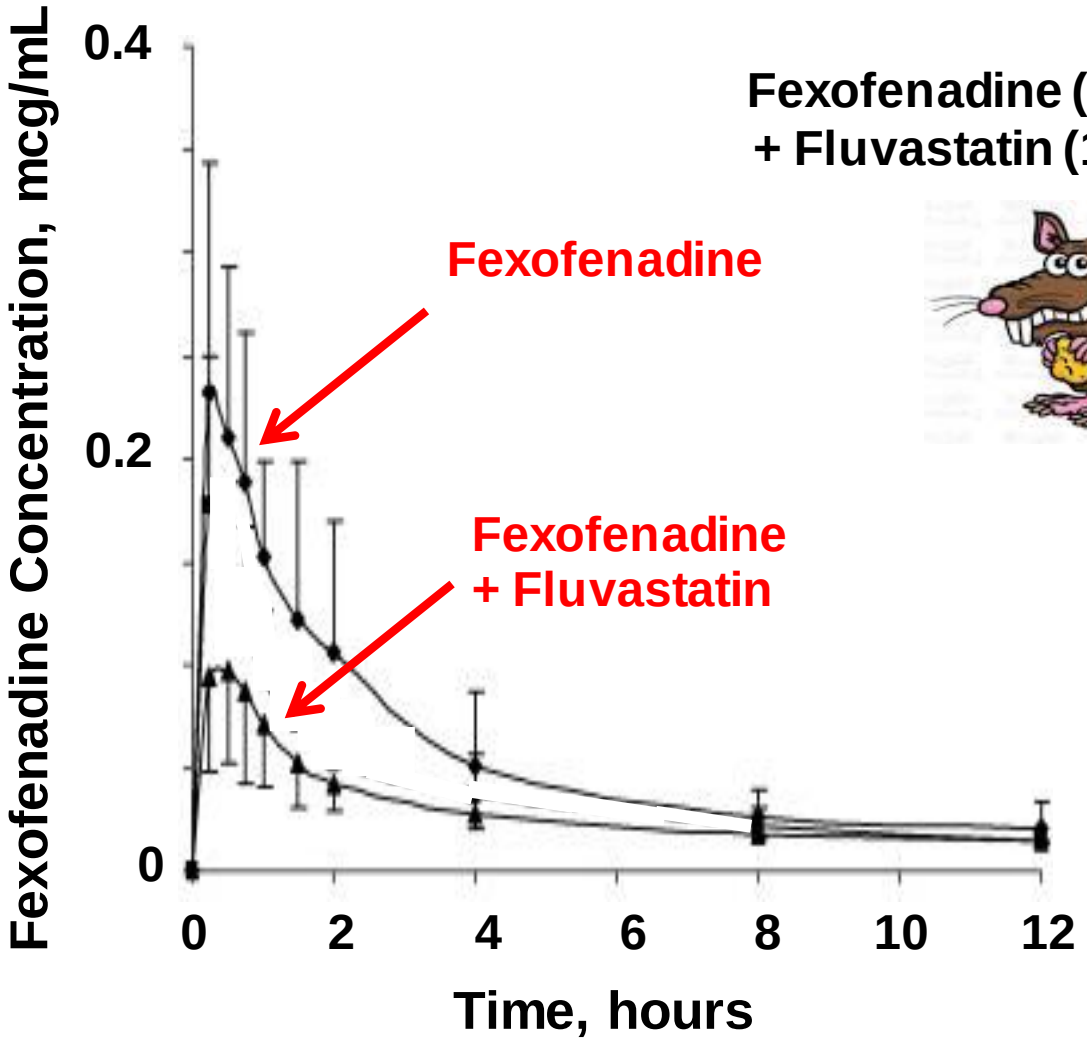
OATPs Are Targets for Drug Drug Interactions



F. Qiang et al., Eur. J. Pharm. Sci, V 37, 2009

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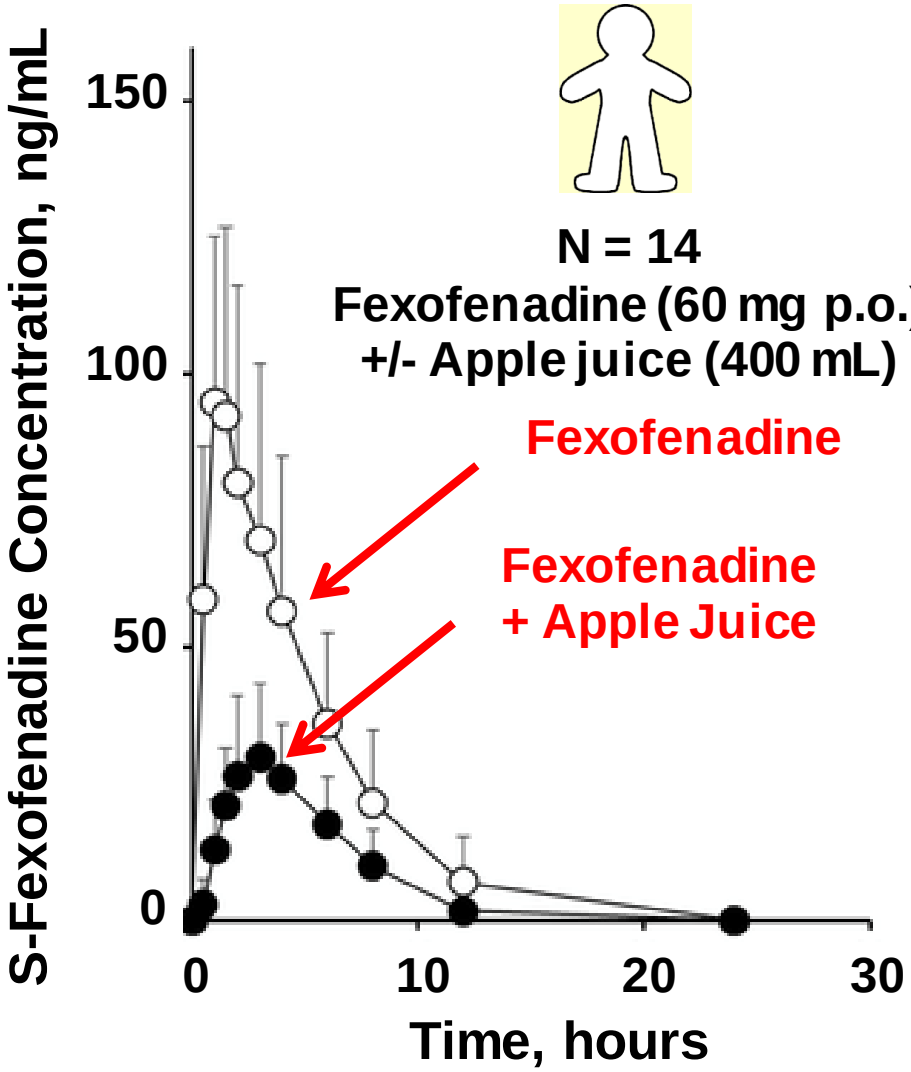
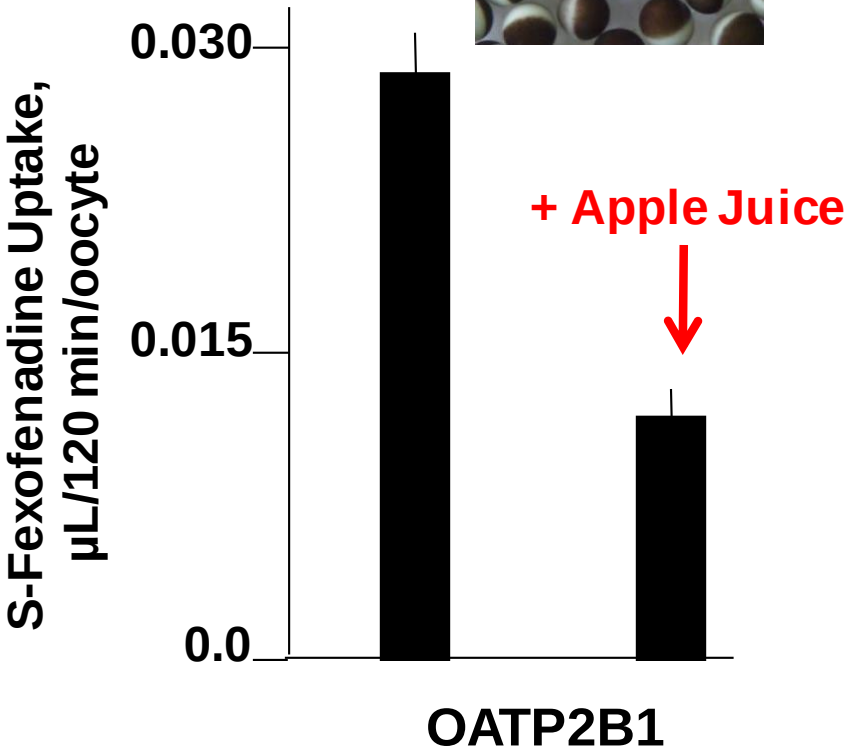
Influence of Apple Juice on Fexofenadine Absorption





Y. Akamine et al., Eur. J. Clin. Pharmacol. , V 70, 2014

Apple Juice: phloridzin, phloretin, hesperidin, quercetin

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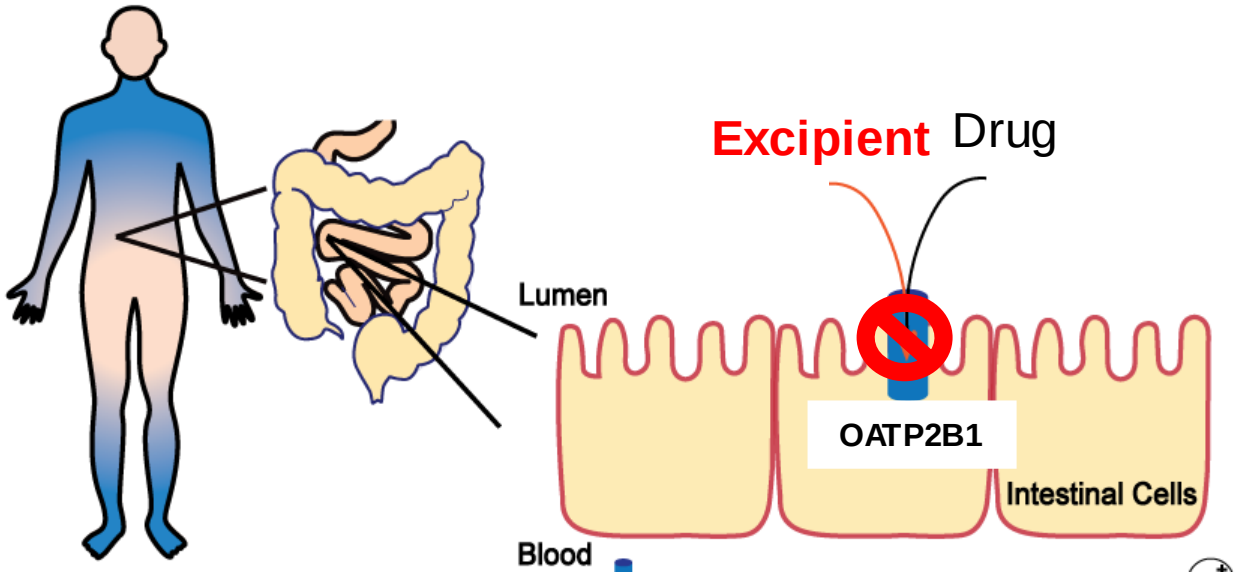
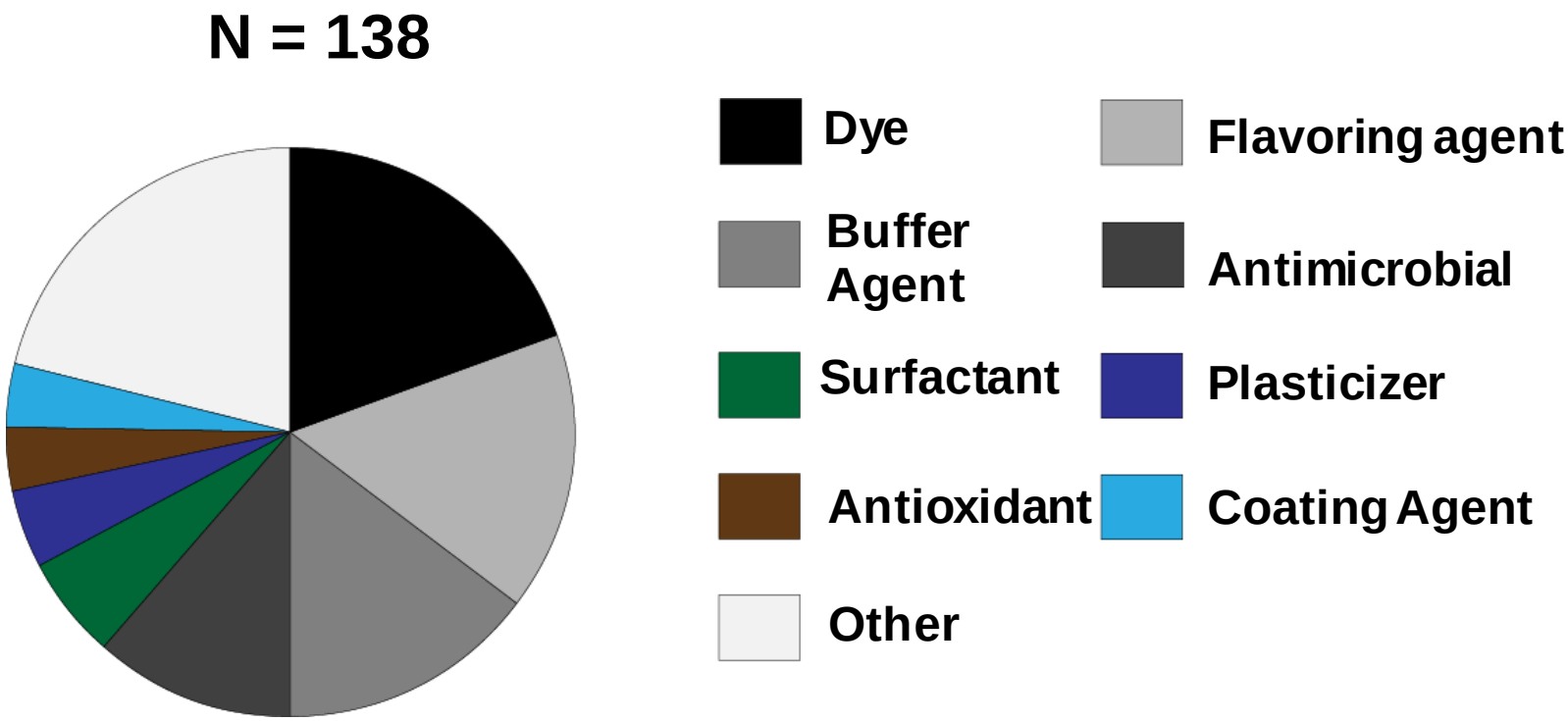
Goal: To determine whether **excipients** used in oral drug products can inhibit OATP2B1



Classification of 138 Oral Molecular Excipients



CERSI Excipient Browser: http://excipients.ucsf.bkslab.org/

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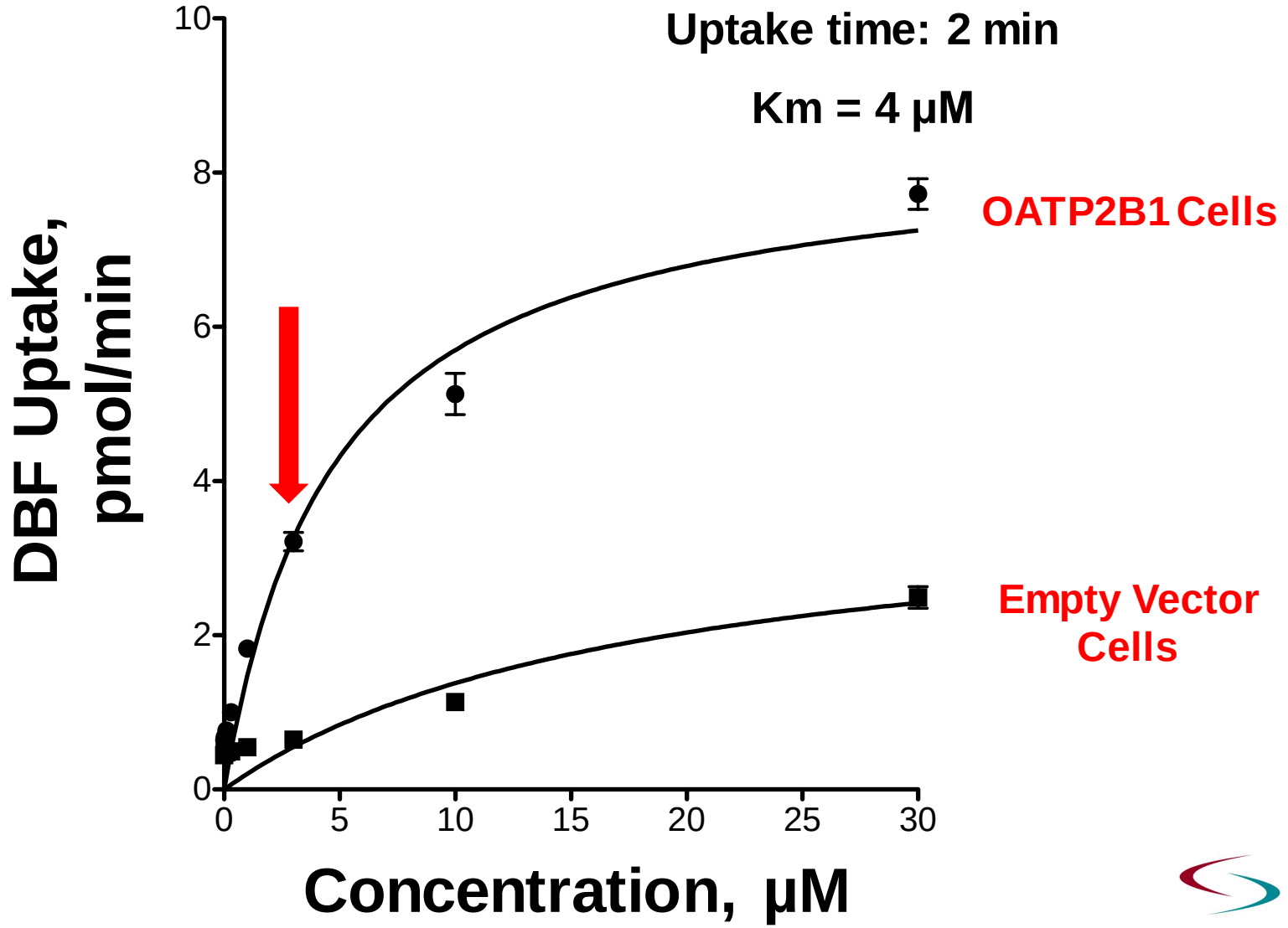
Characterization of OATP2B1-mediated Dibromofluorescein Uptake



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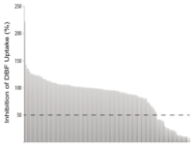
Screen of Oral Excipients for OATP2B1 Inhibitors

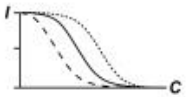
Screen 138 Oral Molecular Excipients

Identified 27 Inhibitors (> 50%)



Conduct Aggregation Tests

Conduct IC_{50} Studies



Potential Clinical Relevance

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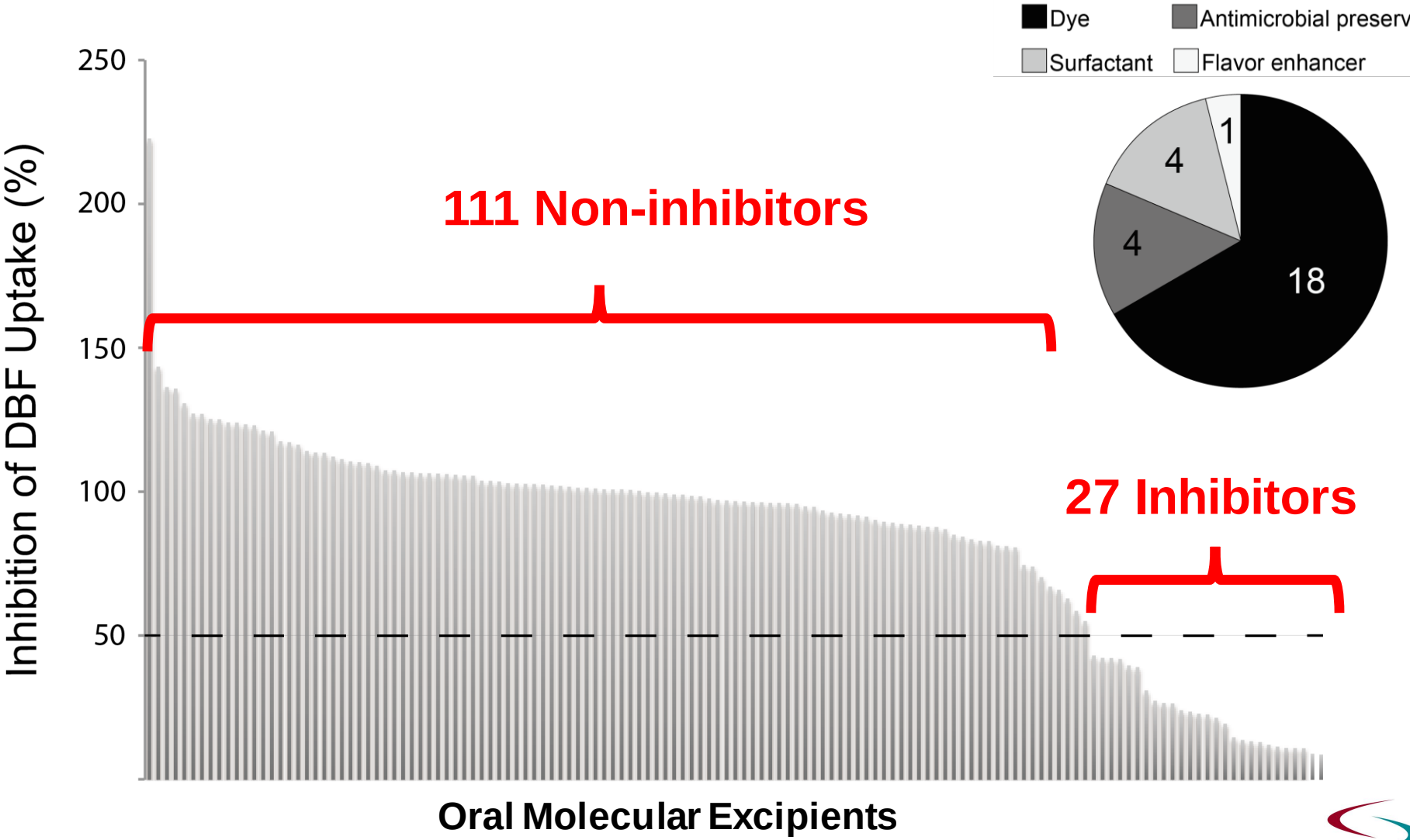
Summary of the Inhibitory Effect of 138 Oral Molecular Excipients



DBF concentration: 2 μM
Uptake time: 3 min

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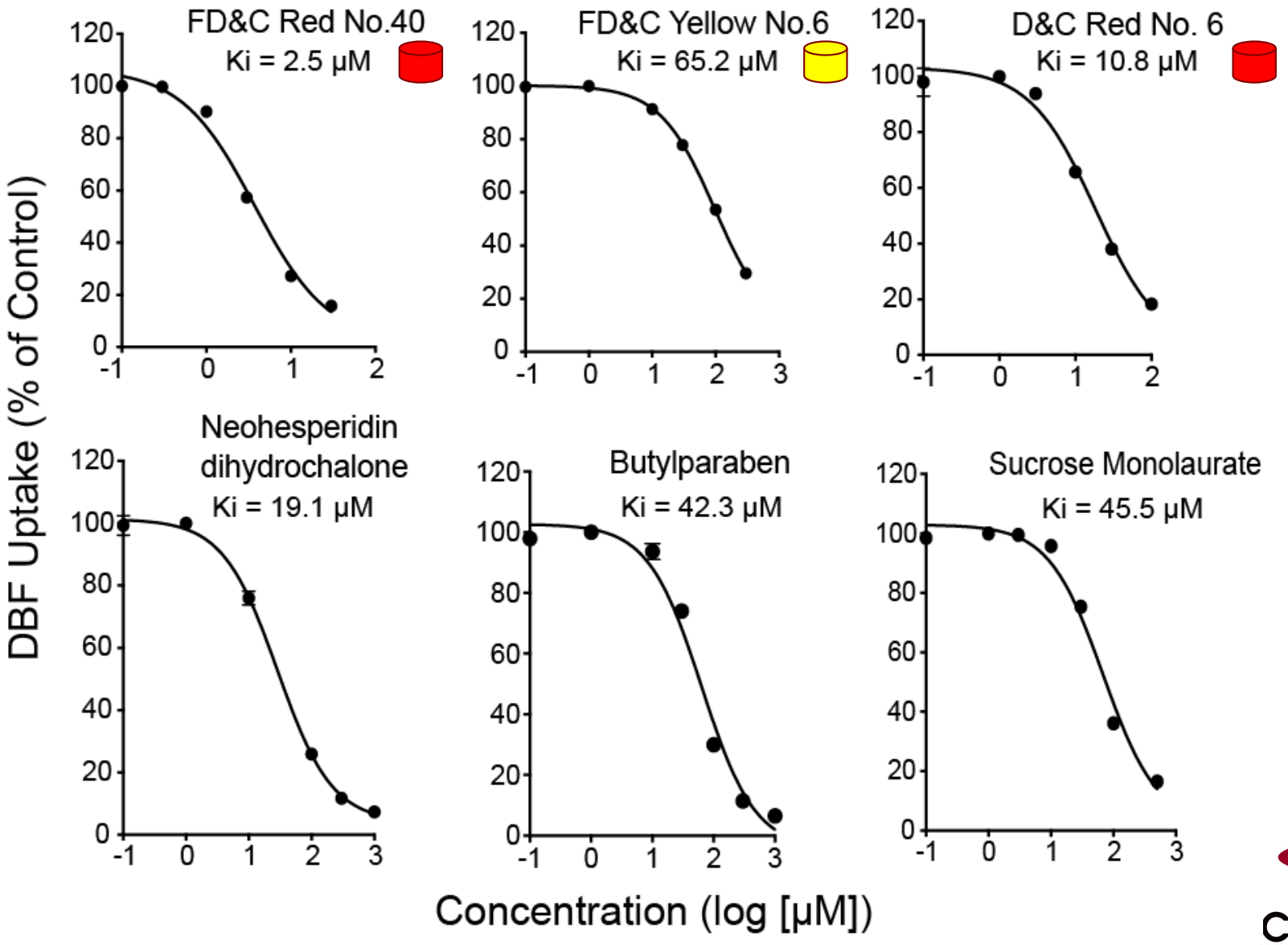
IC_{50} Studies of Selected Excipients Identified as OATP2B1 Inhibitors



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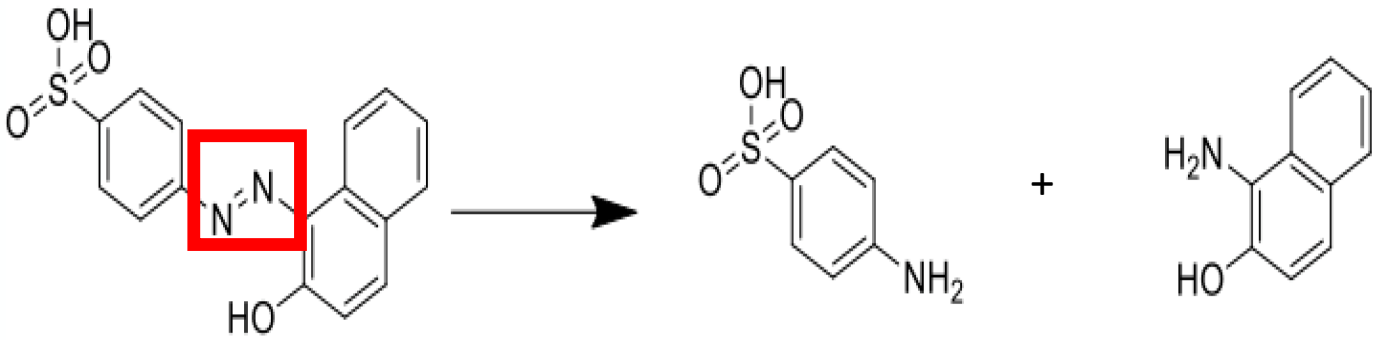
OATP2B1 Inhibitory Potencies of Excipients: Dyes are most potent

Excipient	Ki (μM)	Ki (95% Confidence Intervals)	Aggregation
FD&C Red No. 40	2.47	1.83 – 3.33	No Aggregation @ 500 μM
FD&C Orange No. 4	2.02	1.77 – 2.29	No Aggregation @ 100 μM
Sodium Lauryl Sulfate	1.88	1.31 – 2.72	No Aggregation @ 50 μM
FD&C Green No. 5	1.47	1.13 – 1.92	No Aggregation @ 5 μM
FD&C Red No. 28	0.96	0.62 – 1.5	No Aggregation @ 10 μM
FD&C Red No. 3	0.84	0.66 - 1.06	No Aggregation @ 500 μM
Light Green CF Yellowish	0.77	0.69 – 0.85	No Aggregation @ 200 μM
Guinea green b	0.73	0.61 – 0.87	No Aggregation @ 5 μM
D&C Red No. 27	0.73	0.43 - 1.25	No Aggregation @ 5 μM
Naphthol blue black	0.38	0.31 - 0.47	No Aggregation @ 5 μM

Several Dyes Have Azo Bonds that are Subject to Reduction by Intestinal Bacteria



D&C Orange No. 4

4-aminobenzene sulfonic acid

1-amino-2-naphthol

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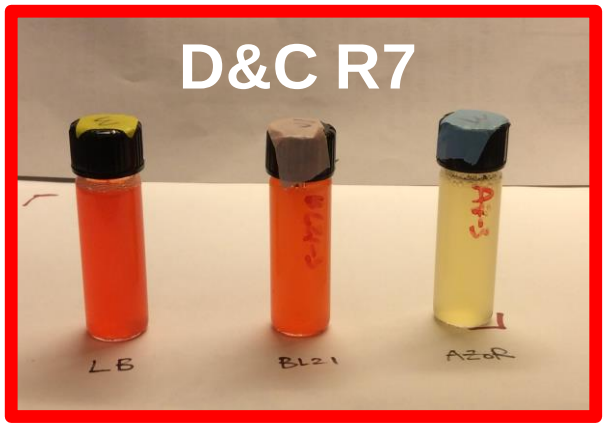
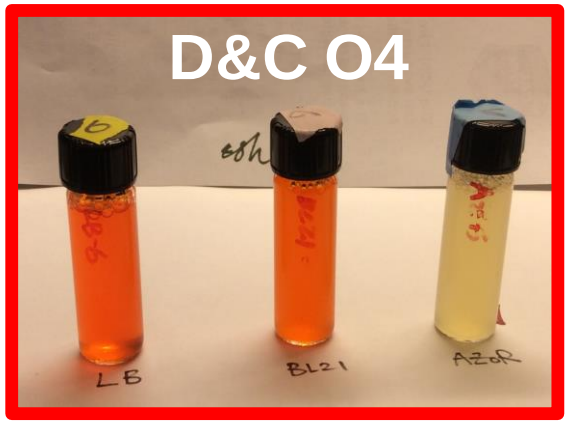
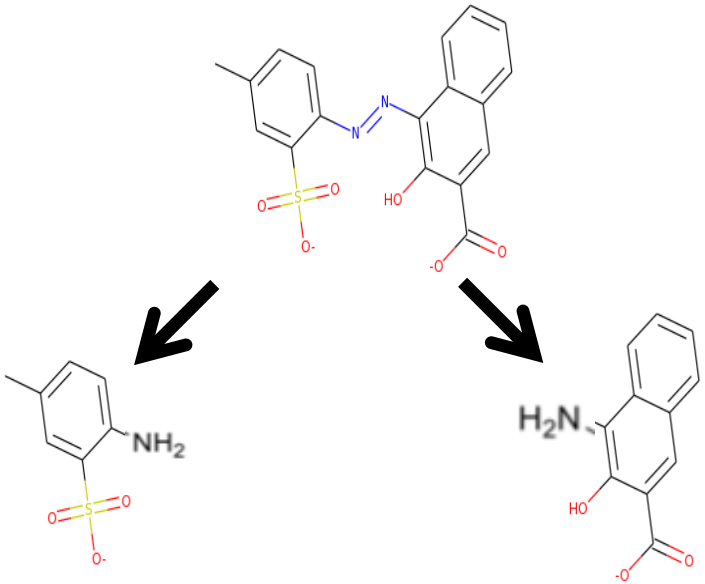
E. Coli Transformed with *AzoR* Reduce Dyes 48 Hours After Incubation

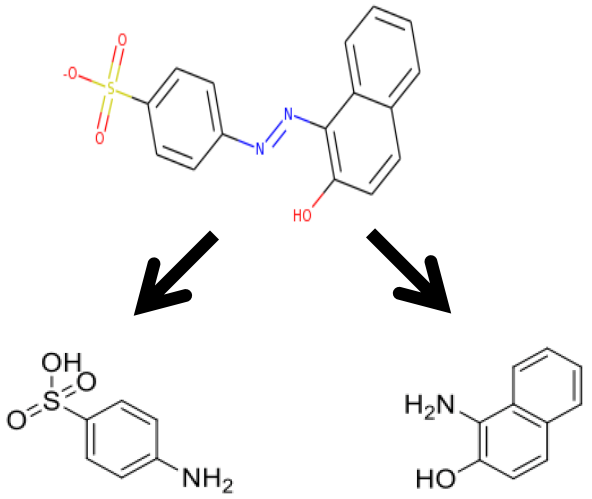


Broth E.Coli E.Coli AzoR



Broth E.Coli E.Coli AzoR





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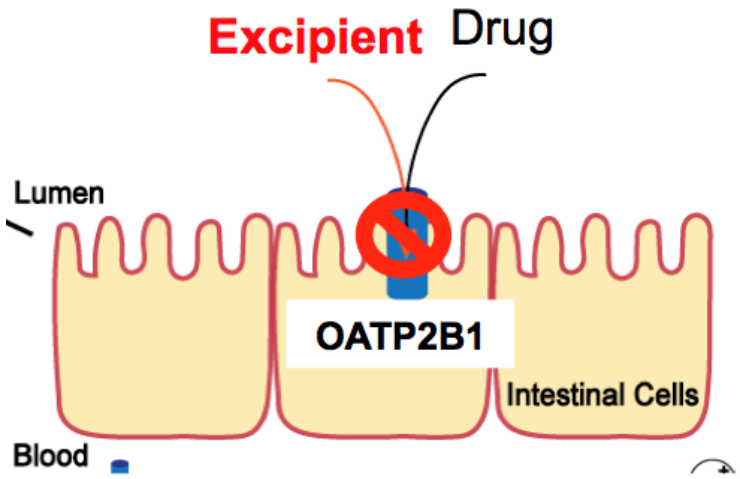
Do the reduced metabolites inhibit OATP2B1?



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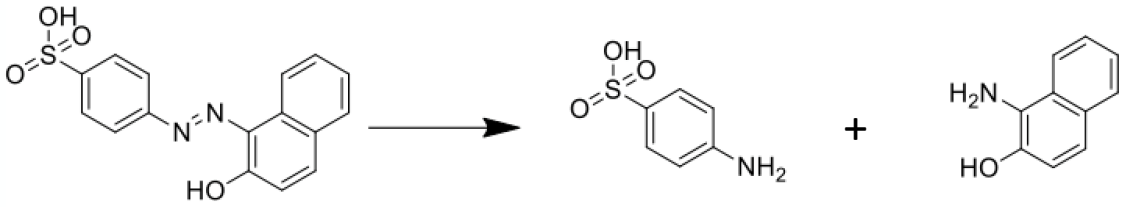
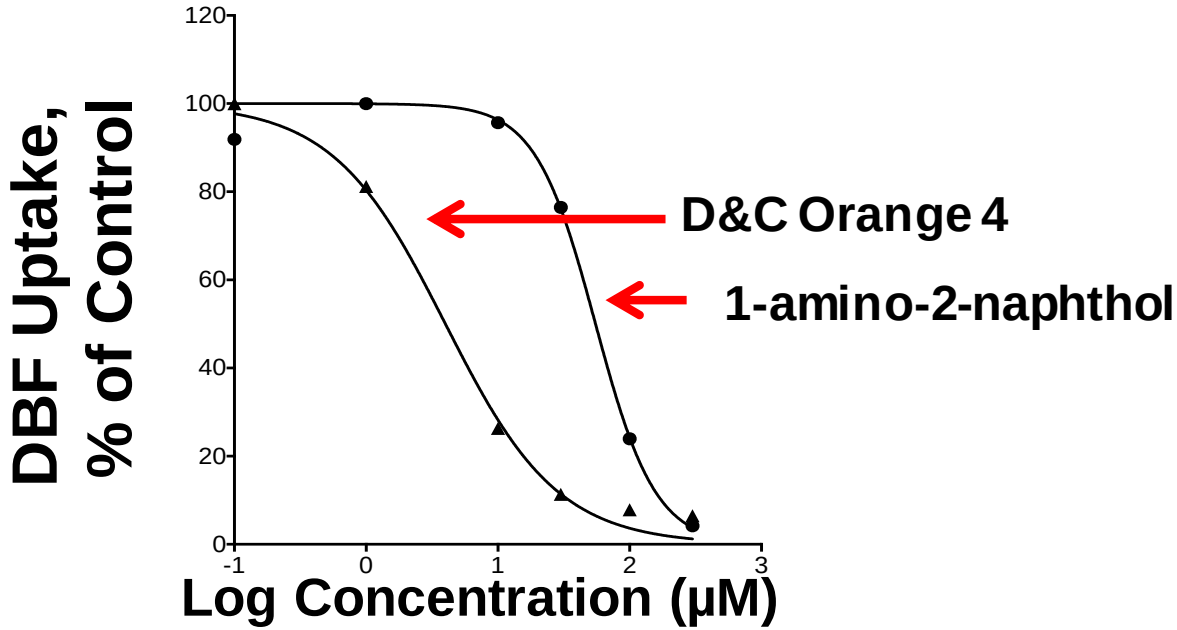
D&C Orange No. 4 is a More Potent Inhibitor of OATP2B1 than Its Reduced Metabolites



D&C Orange No. 4

4-aminobenzene sulfonic acid

1-amino-2-naphthol



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Ki Values for Inhibition of OATP2B1 is Much Higher for the Reduced Metabolites

Excipient	K_i (μM)	K_i (μM)	
		Metabolite 1	Metabolite 2
FD&C Yellow No. 6	65.2	> 200	> 200
D&C Red No. 33	55.4	> 50	> 200
D&C Red No.7	10.8	> 200	> 200
D&C Brown No.1	3.0	> 200	> 200
FD&C Red No.40	2.5	> 50	> 200
D&C Orange No. 4	2.0	> 200	62.5

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Bacteria in Intestine May Reduce the Dyes and

Inactivate Dyes as Inhibitors of OATP2B1

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Potential *In Vivo* Relevance

$$\text{Estimated Maximum Intestinal Concentration} = \frac{\text{Maximum Allowable Amount}}{\text{250 mL}}$$

Excipient	Max Amount	Predicted Max. Gut Con. (μM)	K_i (μM)
FD&C Red No. 40	7 mg*	**3950**	**2.3**

* Acceptable Daily Intake (ADI), Data from WHO

Max amount used as surfactant in beverage, CFR 21

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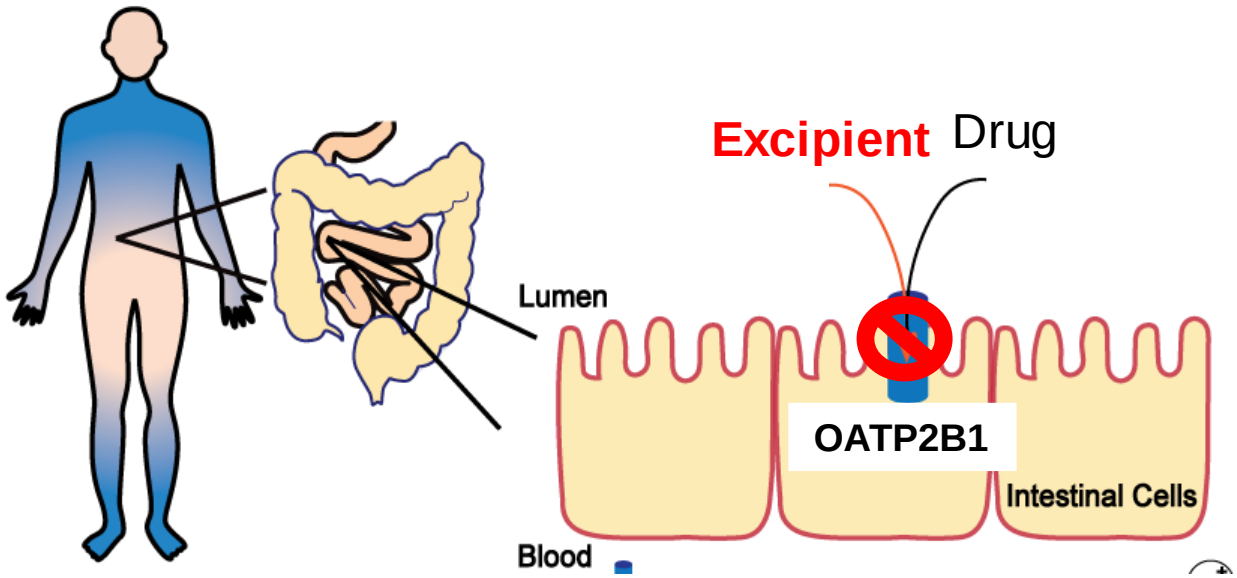
Conclusions

- **27 excipients inhibit OATP2B1, and 111 were deemed "non-inhibitors."**
- **Some excipients are predicted to inhibit OATP2B1 at allowable intestinal concentrations.**
- **Excipients with azo bonds may be reduced by intestinal bacteria and the reduced products are weaker inhibitors of OATP2B1.**
- **The Ki values of excipients will be posted on the CERSI Excipient Browser: http://excipients.ucsf.bkslab.org/.**



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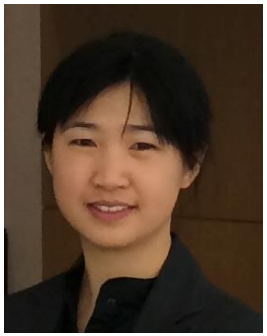
Acknowledgements



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