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"ACS Webinars provide information that is authoritative on topic discussions by field experts and I don't even need to leave my office!"

https://www.acs.org/content/acs/en/acs-webinars/drug-discovery/prodrugs.html

Fan of the Week

Michael K. Riscoe, Ph.D.
Professor, SOM-Molecular Microbiology & Immunology Department,
Oregon Health & Science University,
ACS Member for 22 years strong!

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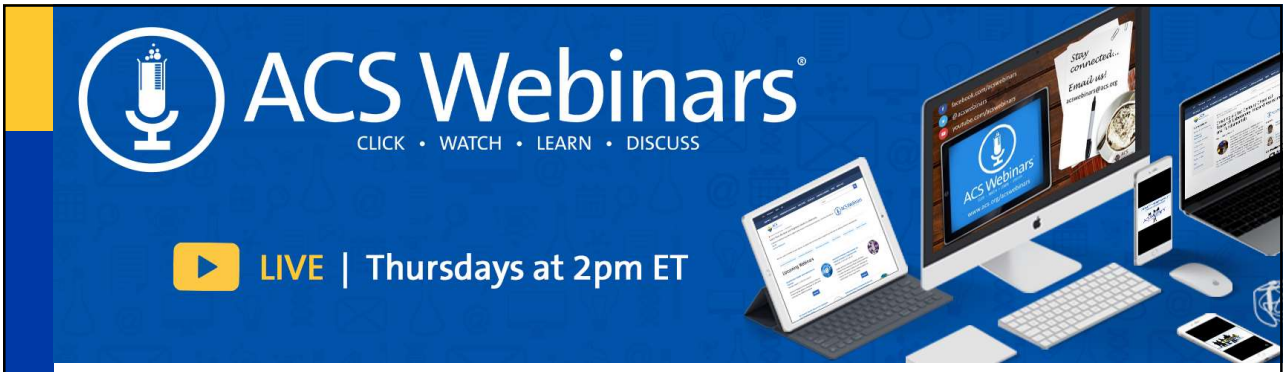

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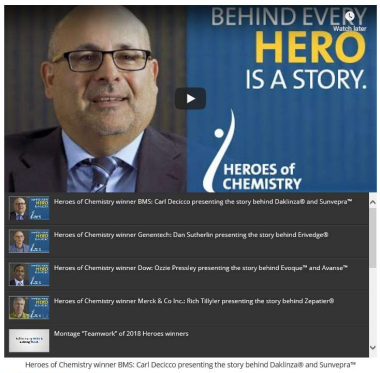
#HeroesofChemistry
ACS Heroes of Chemistry Award

Inspiring Hero Stories



Heroes of Chemistry winner BMS: Carl Decicco presenting the story behind Dakinza® and Sunvepra™

View All Past Recipients >>

*The **ACS Heroes of Chemistry Award** is the Annual award sponsored by the American Chemical Society that recognizes talented industrial chemical scientists whose work has led to the development of successful commercialized products ingrained with chemistry for the benefit of humankind.*

2018 Winners: AstraZeneca, DuPont, Pfizer, SeattleGenetics

www.acs.org/heroes

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An individual development planning tool for you!

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WHO WE ARE

Founded in 1986, the American Association of Pharmaceutical Scientists (AAPS) is a professional, scientific organization of approximately 7,000 individual members and over 10,000 actively participating stakeholders employed in academia, industry, government, and other pharmaceutical science related research institutes worldwide.

Our mission:

To advance the capacity of pharmaceutical scientists to develop products and therapies that improve global health

Our vision:

Advancing the pharmaceutical sciences to drive prevention and cures.

Our five core values:

Learning, Innovation, Service, Inclusiveness and Integrity.

AAPS is incorporated as a not-for-profit organization under the U. S. Internal Revenue Service Code, §501(c)3 in the District of Columbia.

Members of the American Association of Pharmaceutical Scientists (AAPS) gathered during the 2013 AAPS Annual Meeting and Exposition to discuss why they chose a career in pharmaceutical sciences and how AAPS has helped foster their journey. The I Am AAPS video series displays the diversity of AAPS membership while exhibiting one common goal: to impact global health.

https://www.aaps.org

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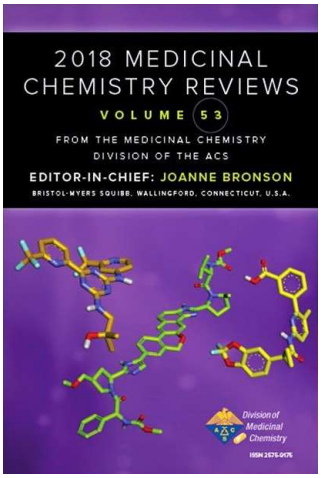

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Celebrating 6 years & 55 Drug Discovery Webinars!

http://bit.ly/acsDrugDiscoveryArchive

ACS Chemistry for Life®

2014

1. Drug Discovery Series #1 - Current Drug Discovery and Development Process
(DDS #1) Watch this overview of the drug discovery and development process to learn the stages and challenges in every step.
2. Primer in Drug Target Classes
(DDS #2) Listen in on a discussion on the big four druggable families and the difference between small molecule and biotherapeutic targets.
3. Key Concepts in Identifying Drug Leads
(DDS #3) Discover how drug-likeness is a deceiving concept, explore the Rule of Five, and show how lessons from the past may guide the present.
4. Lead Optimization – Building Efficacy & Safety
(DDS #4) Learn strategies on how to effectively optimize small molecule hits and rapidly assess your findings.
5. Tips for Filing IND and Starting your Clinical Trials
(DDS #5) What do you need to know when filing for Investigational New Drug submissions to the United States Food and Drug Administration?
6. The Role of Chemistry in Clinical Trials; The Big Expense & Lessons Learned
(DDS #6) Learn how the properties of the candidate impact decisions in the discovery process.
7. Pharmacoeconomics and IP Strategies in Drug Development
(DDS #7) Review the basic principles of Pharmacoeconomics in drug development strategies as well as its role in determining health insurance coverage of drug products.
8. Future of Drug Discovery - Challenges, Risks and Rewards
(DDS #8) Explore how how risks and challenges will be dealt with in the future and the key skill sets required of future medicinal chemists.

2015

- Designing Better Drug Candidates
(January) Learn various factors that can be used to improve candidate quality from Dr. Paul Leeson.
- Strategies to Improve Solubility of Drug Candidates
(February) Learn a number of different strategies for improving drug solubility through structural modification.
- Fragment-Based Drug Design Strategies
(March) Finding the right drug target is becoming increasingly difficult. Learn how focusing on the smaller picture can have big results.
- Screening Strategies
(April) Learn the pros and cons of 6 different screening strategies.
- Avoiding PAINS (pan-assay interference compounds)
(May) Jonathan Baell shares some tips on how to avoid the dead ends of drug discovery.
- Accelerating CNS Positron Emission Tomography (PET) Ligand Discovery
(June) Join Lei Zhang as he lays out a set of preferred parameters for which has yielded successful PET ligands and reduced resources and timelines.
- X-ray Crystallography in Drug Discovery
(July) Jon Mason and Mike Congreve describe what protein-ligand X-ray data can do for you.
- Choices and Trends in Solid Dosage Form Selection
(August) Discover the pros and cons of the different solid state forms and what to consider when selecting.
- Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies
(September) Gain an understanding of acceptable drug delivery approaches to support preclinical dose escalation.
- Pharmacokinetic Considerations in Drug Design and Development
Learn about key pharmacokinetic concepts including clearance, volume of distribution, half life and protein binding.
- Prodrugs in Drug Discovery
(November) John Higgins shares the utility of prodrugs, their general properties and prerequisites for optimal performance.

2016

I - Time: The Fourth Dimension in Drug Discovery

1. The Importance of Drug-Target Kinetics in Drug Design
Robert Copeland - Epizyme, Inc
Dan Erlanson - Carmot Therapeutics
2. Long-Acting Injectable Medications: Strategies and Mechanistic Considerations
Jules Remenar - Alkermes
Annette Bak - Merck
3. Modified Release Formulations for Solubility Starved Compounds
Mengwei Hu - Merck
John Morrison - BMS
4. *The Medicinal Chemist of Tomorrow (Special Topic)*
Joe Barrish - Ashilon
Ravi Nargund - Merck
Molly Schmid - Tech Coast Angels

II - Beyond Traditional Small Molecules

5. Design of Deliverable Macrocycles
Scott Lokey - UC Santa Cruz
Nicholas Meanwell - BMS
6. Dreaming Big and Thinking Small: Applying Medicinal Chemistry Strategy to Antibody-Drug-Conjugates
L. Nathan Tumey - Pfizer
Peter Senter - Seattle Genetics
7. Nucleic Acids Therapeutics: Making Sense of Antisense Oligonucleotides
Punit Seth - Ionis
Richard Olson - BMS
8. Crystallography as a Drug Design and Delivery Tool (Special Topic)
Robert Wenslow - Crystal Pharmatech
Vincent Stoll - Abbvie
Andrew Brunskill - Merck

III - Pharmacology Revisited

9. Dealing with Reactive Drug Metabolites in Drug Discovery: Can We Predict Toxicities of Drug Candidates that form Reactive Metabolites?
Deepak Dalvie - Pfizer
Frederick Peter Guengerich - Vanderbilt University
10. Rational Design of Small Molecules Targeting RNA
Matt Disney - Scripps Fl Florida
Amanda Garner - University of Michigan
11. Cell Penetrating Peptides to Improve Cellular Drug Uptake
Dehua Pei - The Ohio State University
Scott Hart - Bristol-Myers Squibb

2017

I - Fighting Cancer

1. Fighting Cancer: Targeting CNS Malignancy with Kinase Inhibitors
Timothy P. Heffron - Genentech
Mark Wissman - Bristol-Myers Squibb
2. Fighting Cancer: Epigenetic targets for Oncology
Stuart Conway - Oxford
Sharan Bagal - AstraZeneca
3. Fighting Cancer: Allostery and Targeting Cancer Cell Metabolism
Stefan Gross - Agios
Scott Edmundson - AstraZeneca

Special Broadcast

4. Cystic Fibrosis: Discovery of CFTR Modulators
Peter Grootenhuis - Vertex
Nick Meanwell - Bristol-Myers Squibb

II - Anti-infectives

5. Anti-Infectives: Rational Approaches to the Design and Optimization
Jason Sello - Brown University
Courtney Aldrich - University of Minnesota
6. Tuberculosis: An Introduction for Medicinal Chemists
Carl Nathan - Weill Cornell Medicine
Christopher Boyce - Merck
7. Viral Hepatitis: The Search for a Cure
Mike Sofia - Arbutus Biopharma
Stephen Mason - CaroGen Corporation

Special Broadcast

8. Spinal Muscular Atrophy
Kevin Hodgetts - Harvard Medical School
Alyson Weidmann - ACS Publications

III - Immunology

9. Psoriasis: Treatment and Novel Approaches
Frank Narjes - AstraZeneca
John Morrison - Bristol-Myers Squibb
10. Lupus: Treatment and Novel Approaches
Laurence Menard - Bristol-Myers Squibb
Mary Struthers - Bristol-Myers Squibb

2018

- Jan 25 — A New Strategy in Drug Discovery: Protac-Induced Protein Degradation
Ian Churcher - BenevolentBio
Aaron Ballog - Bristol-Myers Squibb
- Feb 22 — Women in Drug Discovery and Development: How to Succeed as a Female in Academia and Industry
Annette Bak - AstraZeneca
Donna Huryn - University of Pittsburgh
Erika Araujo - Bristol-Myers Squibb
Nurulain Zaveri - Astraea Therapeutics
- Mar 29 — A Nanomedicine Overview for mRNA Delivery: Innovative Methods Using Lipid Nanoparticles
Marianna Yanez Arteta - AstraZeneca
Dennis Luerg - Genentech
- Apr 26 — Nanomaterials for Fighting Antibiotic-Resistant Bacteria
Vincent Rotello - University of Massachusetts at Amherst
Christopher England - American Chemical Society
- May 31 — Advanced Nano-Delivery Systems: Facilitating Tumor Delivery and Mitigating Resistance
Mansoor Amiji - Northeastern University
Venkat Krishnamurthy - AstraZeneca
- Jun 28 — Pitfalls and Promise of Central Nervous System Drug Discovery
Valentin Gribkoff - Yale University
Nicholas Meanwell - Bristol-Myers Squibb
- Jul 26 — How to Optimize Central Nervous System Therapeutics: Med Chem Strategies, Tactics, and Workflows
Craig Lindsley - Vanderbilt Center for Neuroscience Drug Discovery
Amy Newman - Intramural Research Program, NIH
- Sept 20 — A Novel Strategy for the Treatment of Chronic Pain: Antagonising PAR2 with a Monoclonal Antibody
Pete Thornton - AstraZeneca
Nurulain Zaveri - Astraea Therapeutics
- Oct 18 — How to Predict Human CNS PK/PD: Preclinical Experiments and Advanced Mathematical Modelling
Elizabeth de Lange - Leiden Academic Center for Drug Research
Alexander Tropsha - University of North Carolina
- Nov 29 — Human Exosomes: An Ideal Vehicle for Delivery of Therapeutic RNAs to Cells and Organs
Hadi Valadi - University of Gothenburg
Alexander Kapustin - AstraZeneca

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2019 Drug Design and Delivery Symposium

http://bit.ly/2019DDDS

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Jan 31	How to Succeed in Drug Discovery: Insight from Medicinal Chemists (1.5 hrs.)	John Lowe III - JL3 Pharm Mark Murcko - Relay Therapeutics Ann Weber - Kallyope William Greenlee - MedChem Discovery Consulting
Feb 28	Cosolvent Molecular Dynamics: Mapping Protein Surfaces to Discover Allosteric Sites	Heather Carlson - University of Michigan Rommie Amaro - UC San Diego
Mar 28	Women at the Interface of Computational Chemistry and Drug Discovery (1.5 hrs)	Zoe Cournia - Biomedical Research Foundation and *JCIM* Kate Holloway - Gfree Bio Yvonne C. Martin - Previously of Abbott Laboratories Shana Posy - Bristol-Myers Squibb
Apr 18	Effective Exploration of Chemical Space in Hit-Finding	Hanneke Jansen - Novartis Institutes for BioMedical Research Zoe Cournia - Biomedical Research Foundation and *JCIM*
May 30	Widening the Therapeutic Window: Kinetic Selectivity and Target Vulnerability	Peter Tonge - Stony Brook University and *ACS Infectious Diseases* Stewart Fisher - C4 Therapeutics
Jun 27	Precision Control of CRISPR-Cas9	Amit Choudhary - Broad Institute of Harvard and MIT Venkat Krishnamurthy - AstraZeneca
Aug 8	Transformation of Recombinant Cells to FDA Approved Products: Clinical Development to Marketplace (New Date)	Rodney Ho - University of Washington Venkat Krishnamurthy - AstraZeneca
Aug 22	The Evolving Outsourcing Landscape in Pharma R&D: Pros and Cons of Different Models	Bart DeCorte - MercachemSyncom Allen Reitz - Fox Chase Chemical Diversity Center
Sep 19	Thinking Outside the Pillbox: Lead Generation and Optimization in Crop Protection Research	Fides Benfatti - Syngenta Tejas Shah - Corteva Agriscience
Oct 24	Treating Diabetes: Designing the Once-Weekly and Oral GLP-1 Semaglutide	Jesper Lau - Novo Nordisk A/S Puneet Tyagi - AstraZeneca
Nov 26	Prodrug Strategies in Medicinal Chemistry	Jarkko Rautio - University of Eastern Finland Victor Guarino - Bristol-Myers Squibb

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Meet the Organizers


Annette Bak
AstraZeneca
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Nicholas Meanwell
Bristol-Myers Squibb
ACS MEDI


Janice Silverman
American Chemical Society


John Morrison
Bristol-Myers Squibb
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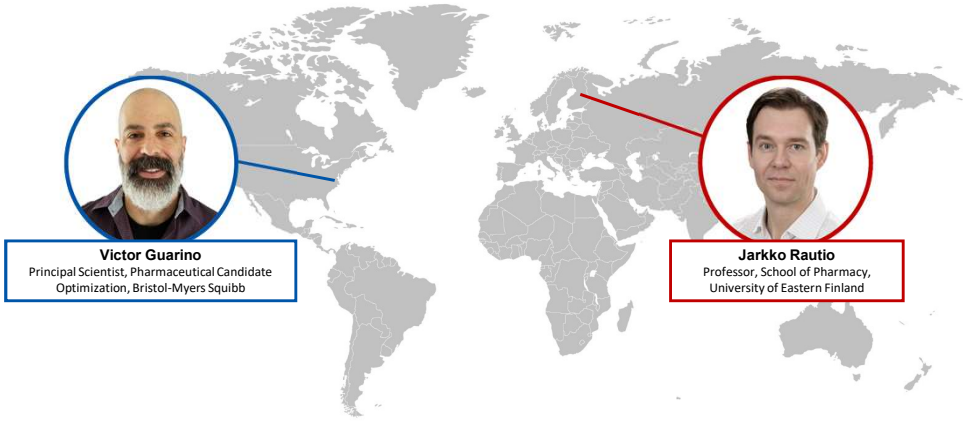
Prodrug Strategies in Medicinal Chemistry



Victor Guarino
Principal Scientist, Pharmaceutical Candidate Optimization, Bristol-Myers Squibb

Jarkko Rautio
Professor, School of Pharmacy, University of Eastern Finland

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Prodrug Strategies in Medicinal Chemistry

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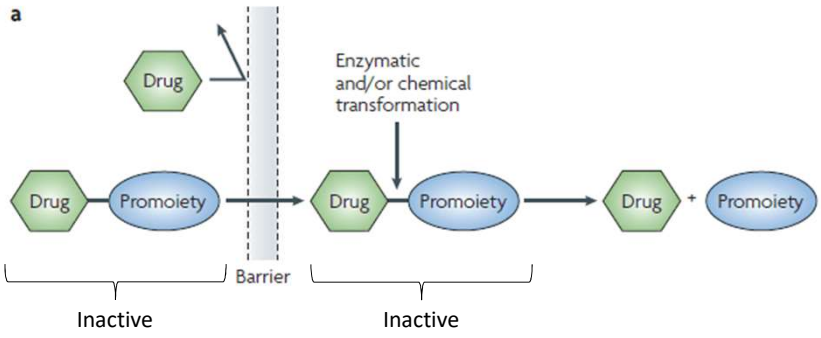
What you will learn

- Introduction to the prodrug concept
- Prodrugs addressing ADMET issues
  - ✓ Improving solubility - formulation
  - ✓ Improving oral absorption - solubility, lipophilicity
  - ✓ Reducing toxicity (controlled release, site-selective conversion, targeted drug delivery)
- Prodrug prevalence
- Challenges and considerations using prodrugs

Simplified prodrug concept



Rautio *et al.* Prodrugs - design and clinical applications.
Nature Reviews Drug Discovery 7: 255-270, 2008

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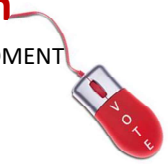
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

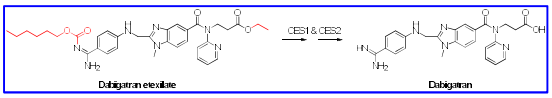


Which can be classified as prodrugs? (Select all the correct answers that apply)

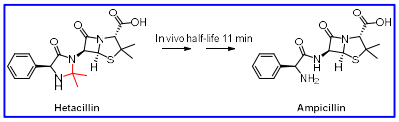
- Drugs having two or more similar promoieties
- Drugs having two or more different promoieties
- Lactone forms
- Drugs undergoing phosphorylation
- None of the above

** If your answer differs greatly from the choices above tell us in the chat!*

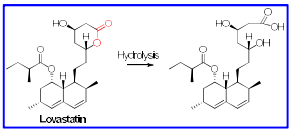
Broader space for prodrug design



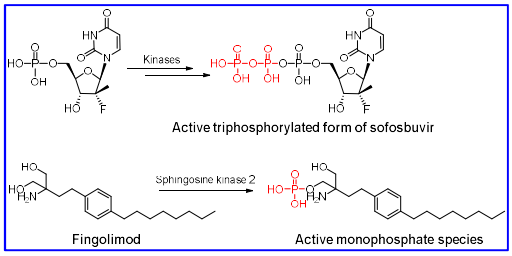
Addition of multiple promoieties (increase in MW)



Addition of promoiety through multiple attachments (increase in MW)

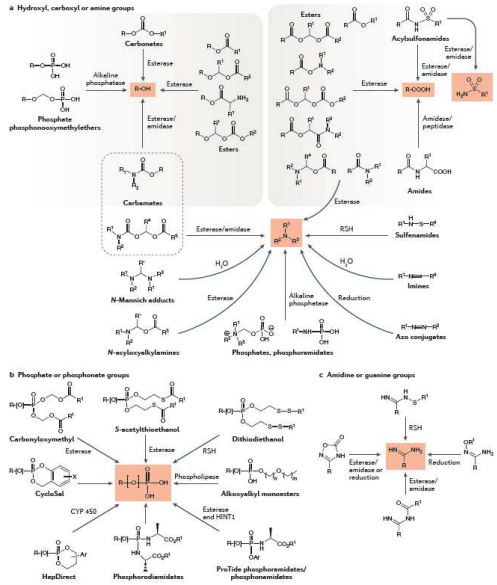


Rearrangement with no promoiety attachment (decrease in MW)



Subtraction of atoms – depends on later addition of groups (decrease in MW)

Prodrug strategies for common functional groups



Consider these:

- **KNOW YOUR PARENT DRUG** - What is the purpose of prodrug derivatization?
- Which functional groups are amenable to derivatization?
- Can the prodrug be readily synthesized?
- The promoiety should be safe and rapidly excreted from the body.
- Chemical modifications made must be reversible.
- Can bioavailability in humans predicted, with a high degree of certainty, using preclinical animal models?
- The absorption, distribution, metabolism, excretion (ADME) properties of parent drug and prodrug require a comprehensive understanding.

Rautio et al. Nature Reviews Drug Discovery 17: 559-587, 2018
Rautio & Laine. In: Textbook of Drug Design and Discovery. 5th Ed. 2017
Stella. J Pharm Sci 99: 4755-4765, 2010

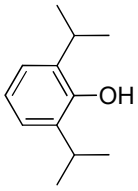
Rationale for prodrug design

- **Better drug formulation and administration options**
  - ✓ Increased aqueous solubility for liquid dosage forms
  - ✓ Enabling new administration routes
- **Improved properties related to ADMET**
  - **Absorption ("A")**
    - ✓ Increased solubility
    - ✓ Improved permeability
  - **Distribution ("D")**
    - ✓ Enabling e.g. brain delivery
  - **Metabolism and excretion ("M" and "E")**
    - ✓ Decreased pre-systemic metabolism
  - **Toxicity ("T")**
    - ✓ Better targeting
    - ✓ Decrease in abuse potential
- **Life-cycle management**
  - ✓ Additional intellectual property (IP)

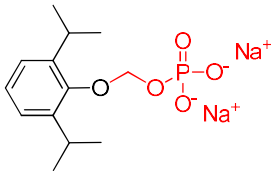
Increased solubility for better IV formulation

Addition of ionized phosphate promoiety

Propofol
(e.g., Diprivan)



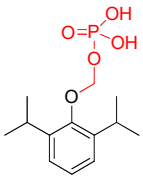
- Anesthetic
- Aq. sol. = 0.13 mg/ml at pH 7.4
- Formulation: O/W emulsion
- Pain at the injection site
- Prone to bacterial contamination
- High lipid content can result in hyperlipidemia with long-term administration
- Onset of action 40 s – 1 min
- Duration of action after bolus 3-10 min



Fospropofol
(Lusedra)

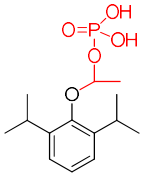
- Approved by FDA in 2008
- Aq. sol. ~500 mg/ml at pH 7.4
- Ready-to-use aqueous solution
- Causes no pain on injection
- Excellent substrate for enzymatic cleavage → onset of action 4-8 min
- Duration of action after bolus 5-18 min
- Excellent synthesis yields

Phosphate esters for alcohols and phenols



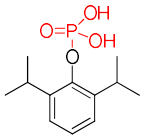
Phosphonooxymethyl propofol (Aquavan®)

- Converted by alkaline phosphatases and chemically
- Releases formaldehyde as a byproduct
- Chemically stable
- T_{max} in rats after IV dose is 3.7 min
- Half-life in humans ~5 min



Ethylidene phosphate prodrug of propofol

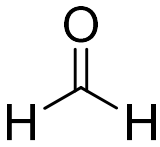
- Converted by alkaline phosphatases and chemically
- Releases acetaldehyde as a byproduct
- Introduces a chiral center
- *In vitro* half-life in alkaline phosphate solution is ca. 20 s.
- Stability in borate buffer at room temperature is 5.2 days – stability problems with some "oxoethylphosphates")
- T_{max} in rats after IV dose is 2.1 min



Propofol phosphate

- Converted by alkaline phosphatases
- Delayed T_{max} in rats after IV dose is 7.3 min

You should NOT be concerned about formaldehyde!

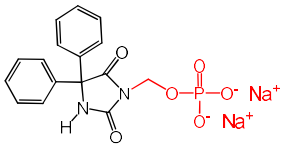


- Exposure to large amounts of formaldehyde vapor can irritate the nasal mucosa and may potentially be carcinogenic
- Gives a positive Ames test
- FDA requires own safety for drugs/prodrugs generating formaldehyde and that cannot be related on historical precedence (tenofovir disoproxil, fosphenytoin, fospropofol etc.)
- Compared to the total amount of daily endogenous formaldehyde production from metabolism, and exogenous exposure from food and the environment (30-60 g/day), the amount generated by prodrugs is minute and is unlikely to cause any systemic toxicity in humans (fospropofol generates 0.050 g/dose formaldehyde – two glasses of red wine generate 0.040 g/day methanol/formaldehyde)

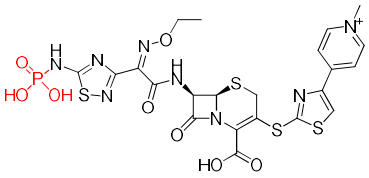
Dhareshwar & Stella. J Pharm Sci 97: 4184-4193, 2008

Phosph(on)ates for other functional groups

Fosphenytoin
(Cerebyx)

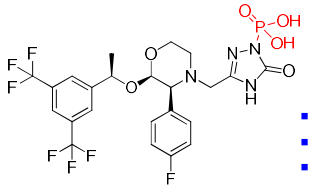


- Increased aqueous solubility from 20-25 µg/mL of phenytoin to 140 mg/mL of fosphenytoin



Cefraroline fosamil (Teflaro)

- *N*-phosphono prodrug
- Increased aqueous solubility from 2.3 mg/mL to >100 mg/mL
- Conversion in plasma at a rate that allows detection of intact prodrug
- FDA approval in 2010

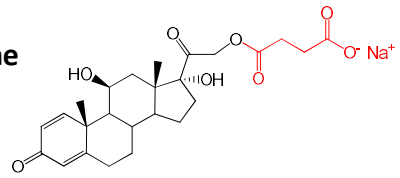


Fosaprepitant
(Emend)

- *N*-phosphonoamino prodrug
- Increased solubility from 0.2 µg/mL to 12 mg/mL
- Rapid conversion in the liver
- An antiemetic drug
- FDA approval in 2008

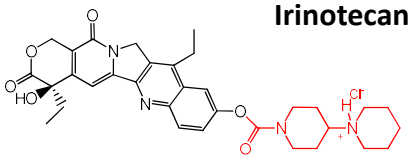
Other solubilizing promoieties for IV use

Prednisolone succinate

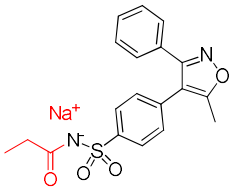


- Succinates are reasonable chemically unstable → must be powders for reconstitution
- Do not convert rapidly and completely *in vivo* → as much as 15% can be excreted unchanged in the urine after iv dose
- Limited solubility in the pH range of optimal ester stability → stability best at low pH values (3-4)
- Also chloramphenicol and methylprednisolone succinates in clinic

Irinotecan



- Dipiperidino carbamate prodrug for IV administration
- Increased aqueous solubility from 2-3 µg/mL (in water) of camptothecin derivative (SN-38) to 20 mg/mL (at pH 3-4)
- Hydrolysis by CESs and butyrylcholinesterase



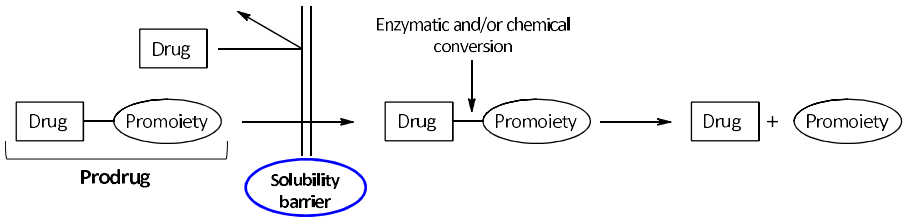
Parecoxib

(Dynastat in Europe)

- First injectable selective COX-2 inhibitor
- Soluble as a sodium form (22 mg/ml)
- Undergoes rapid enzymatic hydrolysis by liver esterases
- Lyophilized powder for reconstitution

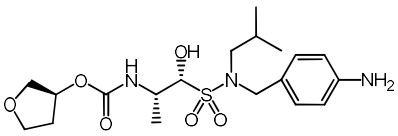
pK_a drops from 9.8 to 4.9

Solubility / dissolution barrier for oral delivery



Only dissolved drug can be absorbed!

Overcoming solubility problems for oral delivery



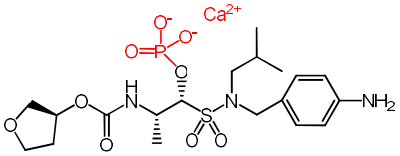
Amprenavir 150 mg soft-gel capsules

Amprenavir

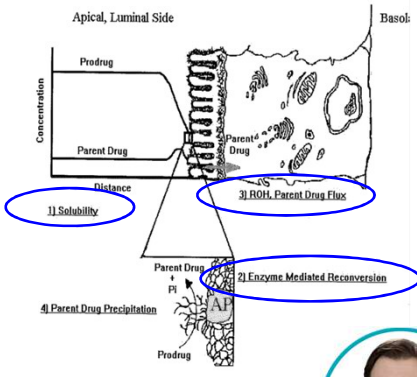
- For the treatment of HIV infection
- Aqueous solubility in water is 0.041 mg/ml
- Good bioavailability (≈ 80%)
- High percentage of excipients (TPGS, PEG-400, PG etc.) due to low solubility requiring 8 capsules two times daily

Only dissolved drug can be absorbed!

Overcoming solubility problems for oral delivery



Fosamprenavir 700 mg tablets



Fosamprenavir (Lexiva®)

- Aqueous solubility in water 0.31 mg/ml (max solubility of calcium salt >100 mg/ml at pH 3-4)
- Biological transformation by brush border gut phosphatase
- Equal bioavailability with amprenavir
- Due to better solubility requires only 2 tablets two times daily
- Patent protection continues longer

Development of fosamprenavir

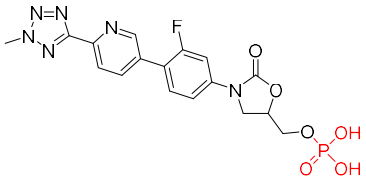
Pros

- Omission of high amount of excipients which reduced pill size and burden
- Fosamprenavir is a NCE – patent expiration later (generic since 2016)
- Previous amprenavir clinical data aided the development and approval of fosamprenavir

Cons

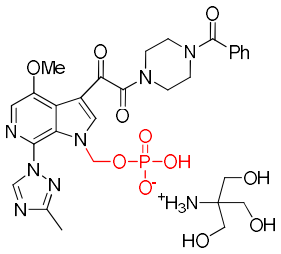
- Full toxicology program completed because small amounts of fosamprenavir enters systemic circulation and new impurities
- PK differences (C_{max} 27% lower), even slight ones, extended clinical development plan from a 1.5-year initial plan to a 3.5-year revised plan

Recent phosphate prodrugs for oral delivery



Tedizolid phosphate (Sivextro)

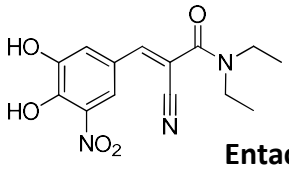
- FDA approval in 2014
- Oral and IV formulation for acute bacterial and skin structure infections



Fostemsavir

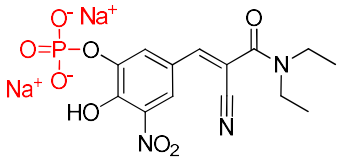
- Completed phase III studies
- Release of the prodrug and subsequent prodrug conversion takes place in the colon

Unsuccessful phosphate prodrugs for oral delivery



Entacapone

- Oral bioavailability ~25-46 %
- Aq. sol. = 17 mg/ml (pH 1.2); 1.75 mg/ml (pH 7.4)
- Assumption was that poor dissolution rate in the pH range of stomach and upper small intestine resulted in low and variable bioavailability



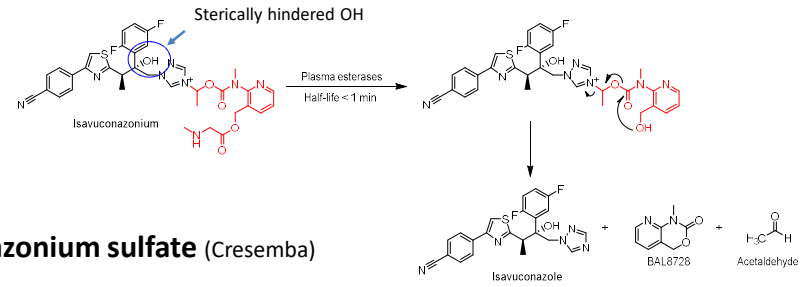
Entacapone phosphate

- Aq. sol. ≥ 30 mg/ml at pH 7.4
- Chemically stable
- Rapidly cleaved by alkaline phosphatases
- Bioavailability of prodrug less than that of entacapone suspension (pH 7.4)
- Reason for low and variable bioavailability was later discovered to be high presystemic metabolism

Leppänen et al. Bioorg Med Chem Lett 10: 1967-1969, 2000
Heimbach et al. Pharm Res 20: 848-856, 2003

Phosphate prodrug strategy is a potential solution to BCS class II drugs

Novel ionized promoiety to increase solubility



Isavuconazonium sulfate (Cresemba)

- FDA approval on March 2015
- Treatment of invasive aspergillosis and invasive mucormycosis (IV and oral)
- F_{abs} oral is 98% (C_{max} 2-3 hours after single and multiple doses)
- IV prodrug rapidly hydrolyzed in blood to isavuconazole by esterases, predominately by butylcholinesterase
- No circulating prodrug after po dose
- Solubility in water over 100 mg/ml

Cresemba prescribing information. Retrieved on 5 May, 2015
Ohwada et al. Bioorg Med Chem Lett 13: 191-196, 2003

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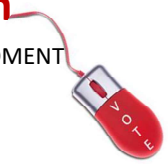
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

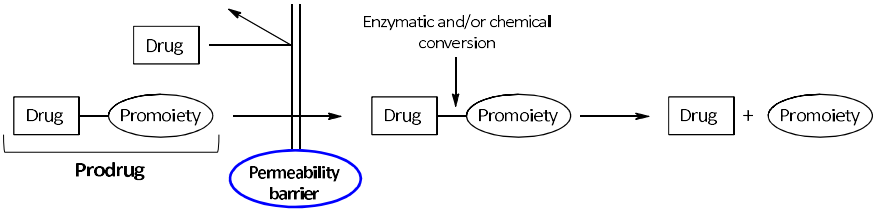


Which barrier can NOT be overcome by a lipophilic prodrug?

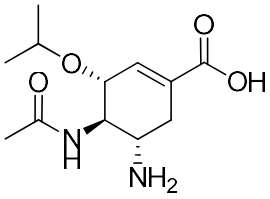
- Intestinal
- Cornea in the eye
- Stratum corneum in the skin
- Blood-brain barrier
- None of the above

** If your answer differs greatly from the choices above tell us in the chat!*

Permeability barrier for oral delivery

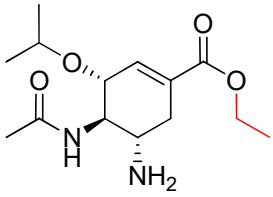


Overcoming poor permeability

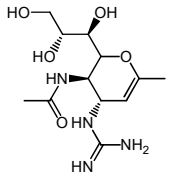


Oseltamivir carboxylate

- Neuramidase inhibitor for influenza A and B
- Exists as a poorly lipophilic zwitterionic amino acid
- Oral bioavailability less than 5 % in preclinical species



Oseltamivir ethyl ester (Tamiflu)

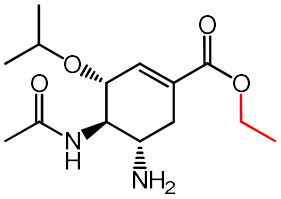


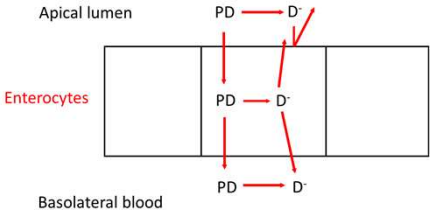
Zanamivir

- Oral bioavailability in humans 80 %
- Bioconverted by carboxylesterases (CES1) in the liver
- Oseltamivir carboxylate is detectable in plasma within 30 min with T_{max} at 3-4 h
- Tamiflu was outselling inhaled zanamivir – the first neuramidase inhibitor on the market – immediately

Species difference in bioconversion rate

Animal species	Compound	Oseltamivir carboxylate % bioavailability
Mouse	Prodrug	30
Rat	Prodrug	35
Dog	Prodrug	73
Human	Oseltamivir carboxylate	4.3
Human	Prodrug	80

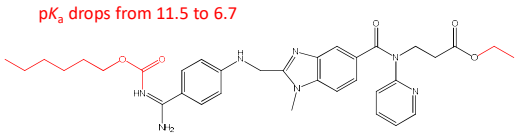




Human GI tract has lower CES activity compared to rodents!

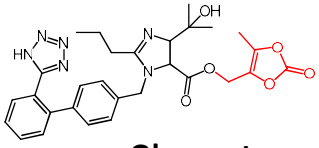
Li et al. Antimicr Agents Chemother 42: 647-653, 1998

Lipophilic prodrugs for oral administration



Dabigatran etexilate

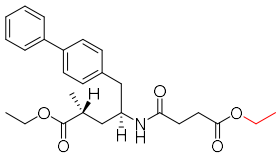
- The oral bioavailability is 3-7% as such but can be increased up to 5-12% by formulation



Olmesartan medoxomil

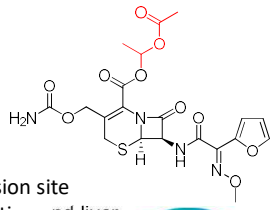
- The oral bioavailability in humans is 26%
- Completely bioactivated during absorption (designed for paraoxonases)

Sacubitril (Entresto)



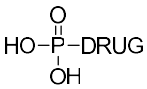
- The oral bioavailability of released sacubitrilat is 41% in monkey, 72% in rat, 77% in dog, and < 50% in humans
- Bioconversion predominantly by CES1

Cefuroxime axetil

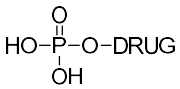


- Steric alleviation of conversion site
- Bioconversion in both intestine and liver
- The oral bioavailability of 36% (fasted) and 52% (fed) in humans

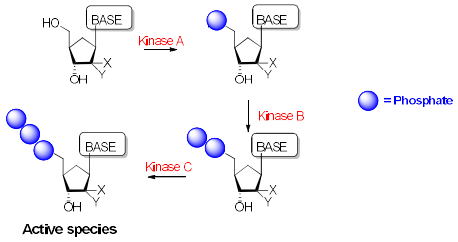
Prodrugs for phosphates/phosphonates



Phosphonate

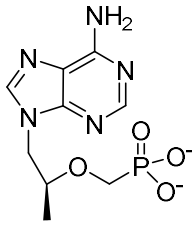


Phosphate



- Nucleoside triphosphate is the active species of nucleoside-based drugs
- Nucleoside phosphorylation to form monophosphate often rate limiting
- Nucleoside analogues are frequently administered as their monophosphorylated forms or configured to include a phosphonate moiety
- Phosphonates and phosphates typically have poor passive permeability - oral bioavailability and intracellular access can be limited
- Can directly form an ester linkage or amidate linkage to attach promoiety
- Can directly attach spacer groups for steric alleviation or adding a conversion trigger
- Four nucleoside monophosphate and monophosphonate prodrugs approved: adefovir dipivoxil, tenofovir disoproxil, tenofovir alafenamide and sofosbuvir

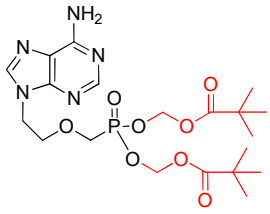
Lipophilic prodrugs of tenofovir



Tenofovir

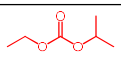
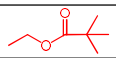
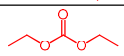
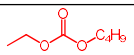
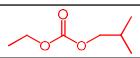
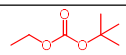
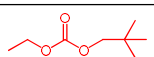
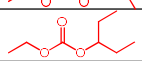
- Acyclic nucleoside phosphonate
- Tenofovir diphosphate is a potent and selective inhibitor of viral reverse transcriptase and effectively blocks viral replication
- Exist as a dianionic at physiological pH
- The log P is less than -3 at pH 6.5

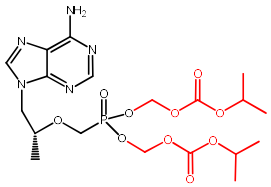
- Demonstrates low and erratic oral bioavailability in animal studies (mice 1.9%, rat 6.0%, monkey 2.7, dog 17.7)
- Adefovir dipivoxil undergoing clinical development was used as a starting point in prodrug discovery project



Adefovir dipivoxil (Hepsera®)

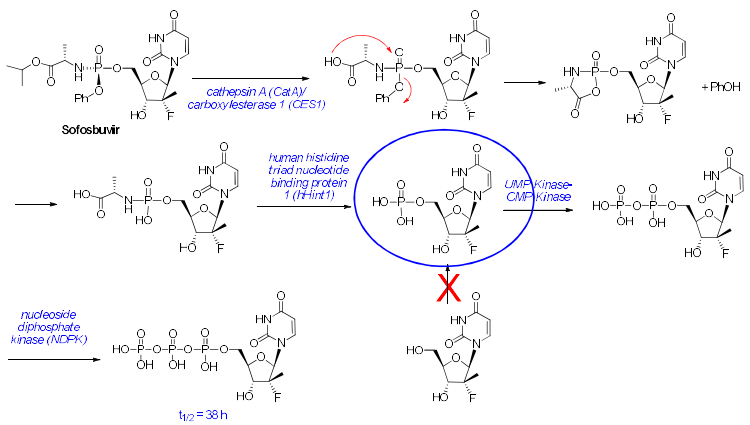
How to select a candidate

Cmpd	Log P pH 6.5	$t_{1/2}$ (hr) pH 7.4	$t_{1/2}$ (min) dog intestinal homog.	$t_{1/2}$ (min) dog plasma	$t_{1/2}$ (min) dog liver homog.	% F in dogs
	1.3	9.2	52.6	20.5	<5	30.1
	2.1	14	10.4	35.5	<5	37.8
	0.6	7.0	23.3	16.6	<5	24.5
	2.7	6.0	<5	<5	<5	18.0
	2.0	9.0	15	<5	<5	20.8
	1.9	0.4	26.6	21.2	14.9	30.7
	>3.0	6.0	<5	<5	<5	16.0
	>3.9	8.0	30	15	<5	28.8



Oral bioavailability of tenofovir in dogs is 17.7%

Phosphoramidate prodrugs for phosphate monoesters

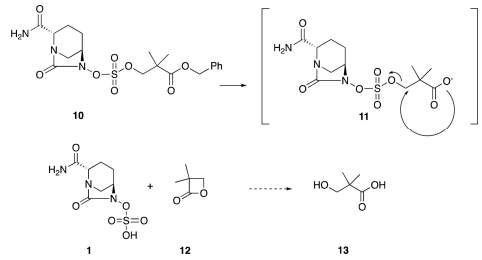


- Phosphoramidate prodrug allows passage across cell membranes
- Enzymatic activity and polarity resulting nucleotide allows intracellular trapping
- Sofosbuvir showed advantageous stability profile for delivery goal:
  - Good stability in simulated gastric and intestinal fluids as well as human plasma
- Sales in 2014 $10.3 billion (initial price tag at $84.000 for a course of Hep-C treatment)

Gilead acquires Pharmasset for $11bn
FINANCIAL TIMES

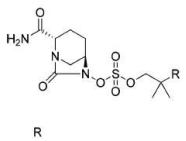
Sofia et al. J Med Chem 53: 7202-7218, 2010
Furman et al. Antiviral Res 120-132, 2011
Chang et al. ACS Med Chem Lett 2: 130-135, 2011

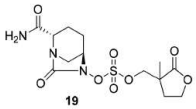
Novel prodrugs of sulfate containing drugs

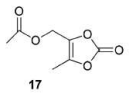


- The first strategy to prepare prodrugs of sulfate containing drugs
- β-lactamase inhibitor avibactam used as an example
  - the oral bioavailability of avibactam was ~1% rat, 15% dog, 3% monkey
- O-neopentyl group and an enzyme triggered nucleophile allow the intramolecular displacement and release of sulfate

Table 1. Bioavailability (F, %) of Prodrugs in Rat, Monkey, and Dog



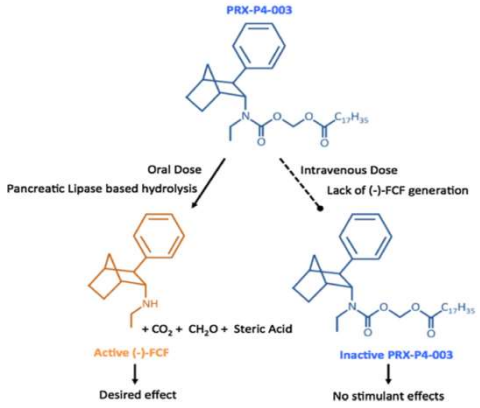


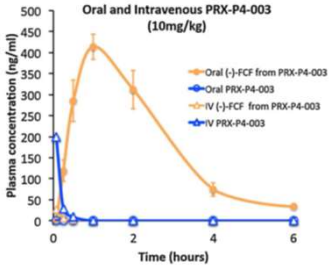


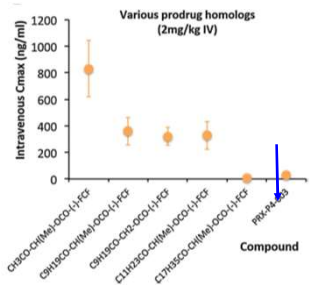
	rat	monkey	dog
14	36	80	100
15	29	60	66
16	37	72	95
17	33	51	86
18	23	33	62
19	36	52	44
20	24	46	34

Gordon et al. J Med Chem 61: 10340-10344, 2018

Site-selective release of an active drug to prevent abuse potential



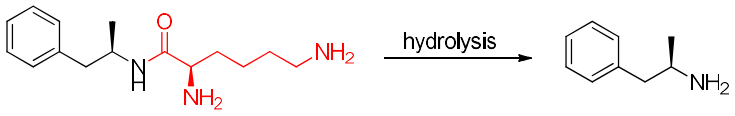




- Fencamfamine is a stimulant having abuse potential if used intravenously
- PRX-P4-003 is a prodrug that is activated in the gut by pancreatic lipases but NOT in plasma

Patil et al. Drug and Alcohol Dependence 186: 159-166, 2018

Controlled release of an active drug to prolong duration of action



Lisdexamphetamine (Vyvance)

Amphetamine

- Lisdexamfetamine was developed with the goal of providing a long duration of effect that is consistent throughout the day, with reduced potential for abuse
- Rapidly absorbed after oral administration - substrate for PepT1
- Converted to dextroamphetamine and L-lysine primarily in blood due to the hydrolytic activity of red blood cells
- Plasma concentrations of unconverted lisdexamfetamine are low and transient, generally becoming non-quantifiable by 8 hours after administration.

Vyvanse Drug Insert. *United States Food and Drug Administration*. Shire US Inc. January 2015. Retrieved 27 April 2015.

Prolonged duration of action - selexipag

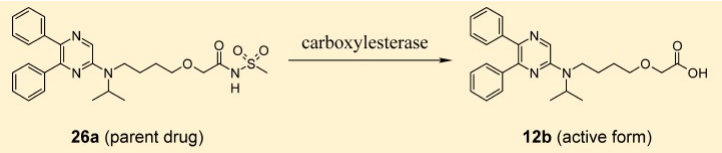


Table 6. Pharmacokinetic Parameters for 12b after Oral Administration of 12b, the Sulfonamides 26a–c, or the Sulfonylurea 26f (1 mg/kg) to Monkeys[a,e]

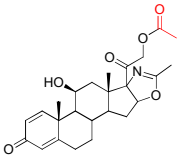
compd administered	compd measured	n	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	$t_{1/2}$ (h)
12b[b]	12b	3	2.3	105	652	5.6
26a	12b	3	14.0	35	859	10.7
	26a	3	6.7	47	384	4.9
26b	12b	2	10	13	170	14.5
	26b	2	10	17	128	2.3
26c[c]	12b	3	4	31	308	8.5
26f[c]	12b	3	6	20	374	*d*

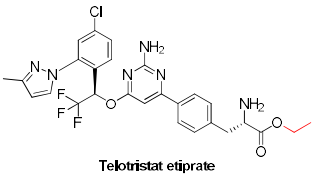
- Oral **selexipag** was approved in 2015 by the FDA for the treatment of pulmonary arterial hypertension
- *N*-acylsulfonamide prodrug is slowly bioconverted by hepatic CES1
- Dose-proportional PK with C_{max} of the parent at 3-4 h after prodrug dose

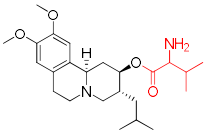
Prodrugs are surprisingly common!

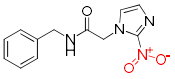
- Currently about 10% of all world-world approved drugs are prodrugs
- 11% of new small molecular entities approved by FDA in 2008-2018 are prodrugs (33/287)
- Recently FDA approved prodrugs are:
  - **2010:** ceftaroline fosamil, dabigatran etexilate, fingolimod
  - **2011:** abiraterone acetate, azilsartan medoximil, gabapentin enacarbil
  - **2012:** tafluprost
  - **2013:** sofosbuvir, dimethyl fumarate, eslicarbazepine acetate
  - **2014:** droxidopa, tedizolid phosphate
  - **2015:** isavuconazonium, sacubitril, uridine triacetate, aripiprazole lauroxil, tenofovir alafenamide, ixazomid, selexipag
  - **2017:** deflazacort, telotristat etiprate, valbenazine, benznidazole, secnidazole, latanoprostene
  - **2018:** fostamatinib, fosnetupitant, baloxavir marboxil

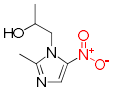
FDA approvals in 2017-2018

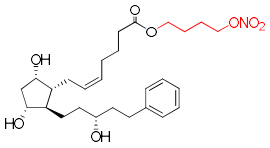

Deflazacort

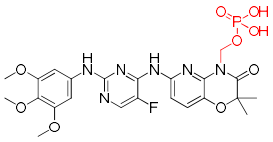

Telotristat etiprate

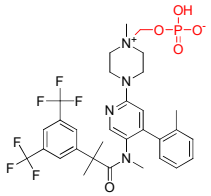

Valbenazine

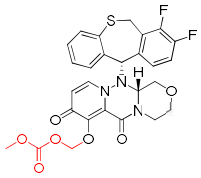

Benznidazole


Secnidazole


Latanoprostene bunod


Fostamatinib


Fosnetupitant


Baloxavir marboxil

Best selling prodrugs

- Tenofovir alafenamide (Genvoya and other combinations), HIV, increased permeation & enhanced intracellular targeting
- Dimethyl fumarate (Tecfidera), multiple sclerosis, increased permeation
- Abitarone acetate (Zytiga), prostate cancer, increased permeation
- Fingolimod (Gilenya), multiple sclerosis, undergoes in vivo phosphorylation → hydroxy form more lipophilic
- Paliperidone palmitate (e.g., Invega Sustenna), mental disorders
- Lamivudine (Triumeq), HIV, hepatitis, undergoes in vivo triphosphorylation → hydroxy form more lipophilic
- Sofosbuvir (Epclusa and other combinations), HCV, increased permeation & enhanced intracellular targeting
- Esomeprazole (Nexium), proton pump inhibitor, masking reactive thiol group
- Dabigatran etexilate (Pradaxa), thrombin inhibitor, increase permeation

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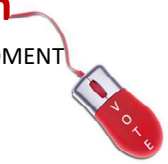
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



What can be the challenges in prodrug discovery and development?

(Select all the correct answers that apply)

- Analytical profiling
- Bioconversion
- Safety of promoieties
- Regulatory control
- None of the above

** If your answer differs greatly from the choices above tell us in the chat!*

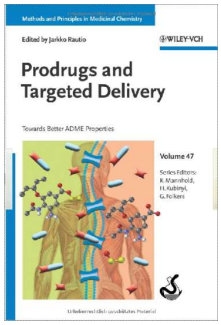
Challenges and considerations in prodrug discovery & development

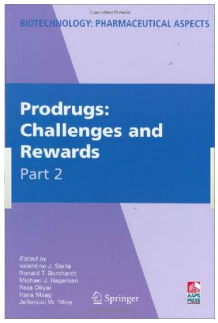
1. Synthesis difficulties
2. More complex analytical profiling
3. Controlling bioconversion and further metabolism
4. Pharmacokinetic studies requiring the analysis of both the prodrug and parent drug
5. Species differences in prodrug conversion
6. Genetic polymorphism and drug-drug interactions regarding prodrug converting enzymes
7. Concerns about the toxicity of not only the prodrug and drug but also the released promoieties or byproducts
8. Navigation of the regulatory environment with prodrugs is far from straightforward, particularly when prodrugs of already marketed active drugs are developed.

What has changed in the past years?

Prodrug intervention has become an integral part of the drug design and discovery strategy!

Further reading





Other excellent reviews on prodrugs:

- Beaumont et al. Curr Drug Metab 4: 461-485, 2003
- Clas et al. Drug Disc Today 19: 79-87, 2014
- Erion et al. Curr Opin Invest Drugs 7: 109-, 2006
- Ettmayer et al. J Med Chem 47: 1-12, 2004
- Huttunen et al. Curr Med Chem 15: 2346-2365, 2008
- Jana et al. Curr Med Chem 17: 3874-3908, 2010
- Maag. Drug Disc Today: Technol 9: 121-130, 2012
- Pradere et al. Chem Rev 114: 9154-9218, 2014
- Stella. J Pharm Sci 99: 4755-4764, 2010
- Stella & Nt-Addae. Adv Drug Deliv Rev 59: 677-694, 2007
- Vig et al. Adv Drug Deliv Rev 65: 1370-1385, 2013

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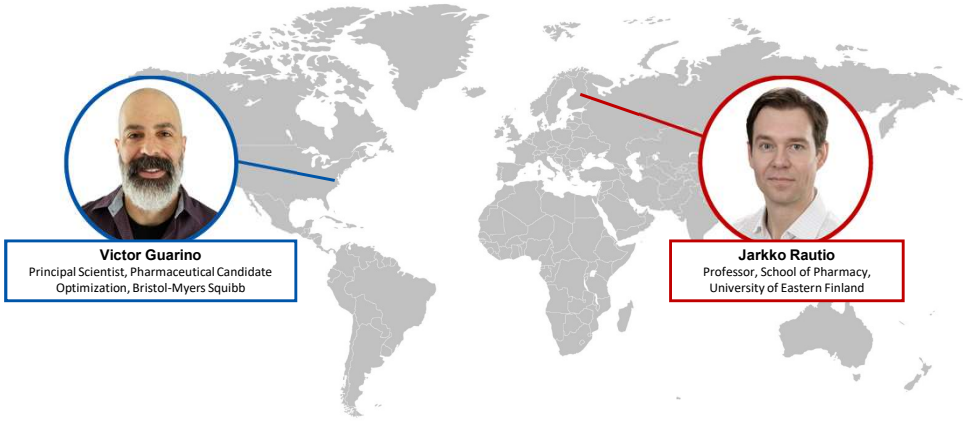

Victor Guarino
Principal Scientist, Pharmaceutical Candidate Optimization, Bristol-Myers Squibb

Jarkko Rautio
Professor, School of Pharmacy, University of Eastern Finland

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(DDS #2) Listen in on a discussion on the big four druggable families and the difference between small molecule and biotherapeutic targets.
3. Key Concepts in Identifying Drug Leads
(DDS #3) Discover how drug-likeness is a deceiving concept, explore the Rule of Five, and show how lessons from the past may guide the present.
4. Lead Optimization – Building Efficacy & Safety
(DDS #4) Learn strategies on how to effectively optimize small molecule hits and rapidly assess your findings.
5. Tips for Filing IND and Starting your Clinical Trials
(DDS #5) What do you need to know when filing for Investigational New Drug submissions to the United States Food and Drug Administration?
6. The Role of Chemistry in Clinical Trials; The Big Expense & Lessons Learned
(DDS #6) Learn how the properties of the candidate impact decisions in the discovery process.
7. Pharmacoeconomics and IP Strategies in Drug Development
(DDS #7) Review the basic principles of Pharmaco-economics in drug development strategies as well as its role in determining health insurance coverage of drug products.
8. Future of Drug Discovery - Challenges, Risks and Rewards
(DDS #8) Explore how how risks and challenges will be dealt with in the future and the key skill sets required of future medicinal chemists.

2015

- Designing Better Drug Candidates
(January) Learn various factors that can be used to improve candidate quality from Dr. Paul Leeson.
- Strategies to Improve Solubility of Drug Candidates
(February) Learn a number of different strategies for improving drug solubility through structural modification.
- Fragment-Based Drug Design Strategies
(March) Finding the right drug target is becoming increasingly difficult. Learn how focusing on the smaller picture can have big results.
- Screening Strategies
(April) Learn the pros and cons of different screening strategies.
- Avoiding PAINS (pan-assay interference compounds)
(May) Jonathan Baell shares some tips on how to avoid the dead ends of drug discovery.
- Accelerating CNS Positron Emission Tomography (PET) Ligand Discovery
(June) Join Lei Zhang as he lays out a set of preferred parameters for which has yielded successful PET ligands and reduced resources and timelines.
- X-ray Crystallography in Drug Discovery
(July) Jon Mason and Mike Congreve describe what protein-ligand X-ray data can do for you.
- Choices and Trends in Solid Dosage Form Selection
(August) Discover the pros and cons of the different solid state forms and what to consider when selecting.
- Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies
(September) Gain an understanding of acceptable drug delivery approaches to support preclinical dose escalation.
- Pharmacokinetic Considerations in Drug Design and Development
Learn about key pharmacokinetic concepts including clearance, volume of distribution, half life and protein binding.
- Prodrugs in Drug Discovery
(November) John Higgins shares the utility of prodrugs, their general properties and prerequisites for optimal performance.

2016

I - Time: The Fourth Dimension in Drug Discovery
1. The Importance of Drug-Target Kinetics in Drug Design
Robert Copeland - Epizyme, Inc
Dan Erlanson - Carmot Therapeutics
2. Long-Acting Injectable Medications: Strategies and Mechanistic Considerations
Jules Remenar - Alkermes
Annette Bak - Merck
3. Modified Release Formulations for Solubility Starved Compounds
Mengwei Hu - Merck
John Morrison - BMS
4. *The Medicinal Chemist of Tomorrow (Special Topic)*
Joe Barrish - Ashilon
Ravi Nargund - Merck
Molly Schmid - Tech Coast Angels

II - Beyond Traditional Small Molecules
5. Design of Deliverable Macrocycles
Scott Lokey - UC Santa Cruz
Nicholas Meanwell - BMS
6. Dreaming Big and Thinking Small: Applying Medicinal Chemistry Strategy to Antibody-Drug-Conjugates
L. Nathan Tumey - Pfizer
Peter Senter - Seattle Genetics
7. Nucleic Acids Therapeutics: Making Sense of Antisense Oligonucleotides
Punit Seth - Ionis
Richard Olson - BMS
8. Crystallography as a Drug Design and Delivery Tool (Special Topic)
Robert Wenslow - Crystal Pharmatech
Vincent Stoll - Abbvie
Andrew Brunskill - Merck

III - Pharmacology Revisited
9. Dealing with Reactive Drug Metabolites in Drug Discovery: Can We Predict Toxicities of Drug Candidates that form Reactive Metabolites?
Deepak Dalvie - Pfizer
Frederick Peter Guengerich - Vanderbilt University
10. Rational Design of Small Molecules Targeting RNA
Matt Disney - Scripps Fl Florida
Amanda Garner - University of Michigan
11. Cell Penetrating Peptides to Improve Cellular Drug Uptake
Dehua Pei - The Ohio State University
Scott Hart - Bristol-Myers Squibb

2017

I - Fighting Cancer
1. Fighting Cancer: Targeting CNS Malignancy with Kinase Inhibitors
Timothy P. Heffron - Genentech
Mark Wissman - Bristol-Myers Squibb
2. Fighting Cancer: Epigenetic targets for Oncology
Stuart Conway - Oxford
Sharan Bagal - AstraZeneca
3. Fighting Cancer: Allostery and Targeting Cancer Cell Metabolism
Stefan Gross - Agios
Scott Edmundson - AstraZeneca

Special Broadcast
4. Cystic Fibrosis: Discovery of CFTR Modulators
Peter Grootenhuis - Vertex
Nick Meanwell - Bristol-Myers Squibb

II - Anti-infectives
5. Anti-Infectives: Rational Approaches to the Design and Optimization
Jason Sello - Brown University
Courtney Aldrich - University of Minnesota
6. Tuberculosis: An Introduction for Medicinal Chemists
Carl Nathan - Weill Cornell Medicine
Christopher Boyce - Merck
7. Viral Hepatitis: The Search for a Cure
Mike Sofia - Arbutus Biopharma
Stephen Mason - CaroGen Corporation

Special Broadcast
8. Spinal Muscular Atrophy
Kevin Hodgetts - Harvard Medical School
Alyson Weidmann - ACS Publications

III - Immunology
9. Psoriasis: Treatment and Novel Approaches
Frank Narjes - AstraZeneca
John Morrison - Bristol-Myers Squibb
10. Lupus: Treatment and Novel Approaches
Laurence Menard - Bristol-Myers Squibb
Mary Struthers - Bristol-Myers Squibb

2018

- Jan 25 — A New Strategy in Drug Discovery: Protac-Induced Protein Degradation
Ian Churcher - BenevolentBio
Aaron Ballog - Bristol-Myers Squibb
- Feb 22 — Women in Drug Discovery and Development: How to Succeed as a Female in Academia and Industry
Annette Bak - AstraZeneca
Donna Huryn - University of Pittsburgh
Erika Araujo - Bristol-Myers Squibb
Nurulain Zaveri - Astraea Therapeutics
- Mar 29 — A Nanomedicine Overview for mRNA Delivery: Innovative Methods Using Lipid Nanoparticles
Marianna Yanez Arteta - AstraZeneca
Dennis Luerg - Genentech
- Apr 26 — Nanomaterials for Fighting Antibiotic-Resistant Bacteria
Vincent Rotello - University of Massachusetts at Amherst
Christopher England - American Chemical Society
- May 31 — Advanced Nano-Delivery Systems: Facilitating Tumor Delivery and Mitigating Resistance
Mansoor Amiji - Northeastern University
Venkat Krishnamurthy - AstraZeneca
- Jun 28 — Pitfalls and Promise of Central Nervous System Drug Discovery
Valentin Gribkoff - Yale University
Nicholas Meanwell - Bristol-Myers Squibb
- Jul 26 — How to Optimize Central Nervous System Therapeutics: Med Chem Strategies, Tactics, and Workflows
Craig Lindsley - Vanderbilt Center for Neuroscience Drug Discovery
Amy Newman - Intramural Research Program, NIH
- Sept 20 — A Novel Strategy for the Treatment of Chronic Pain: Antagonising PAR2 with a Monoclonal Antibody
Pete Thornton - AstraZeneca
Nurulain Zaveri - Astraea Therapeutics
- Oct 18 — How to Predict Human CNS PK/PD: Preclinical Experiments and Advanced Mathematical Modelling
Elizabeth de Lange - Leiden Academic Center for Drug Research
Alexander Tropsha - University of North Carolina
- Nov 29 — Human Exosomes: An Ideal Vehicle for Delivery of Therapeutic RNAs to Cells and Organs
Hadi Valadi - University of Gothenburg
Alexander Kapustin - AstraZeneca

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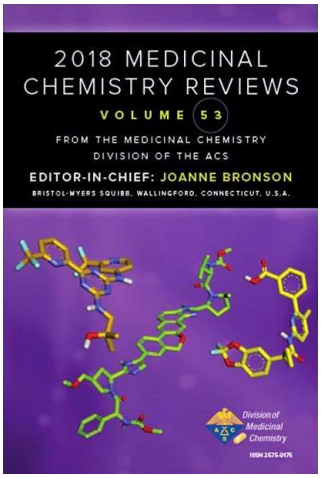

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