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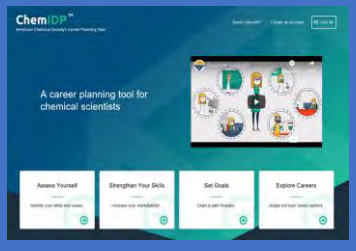

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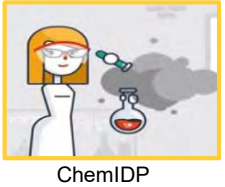
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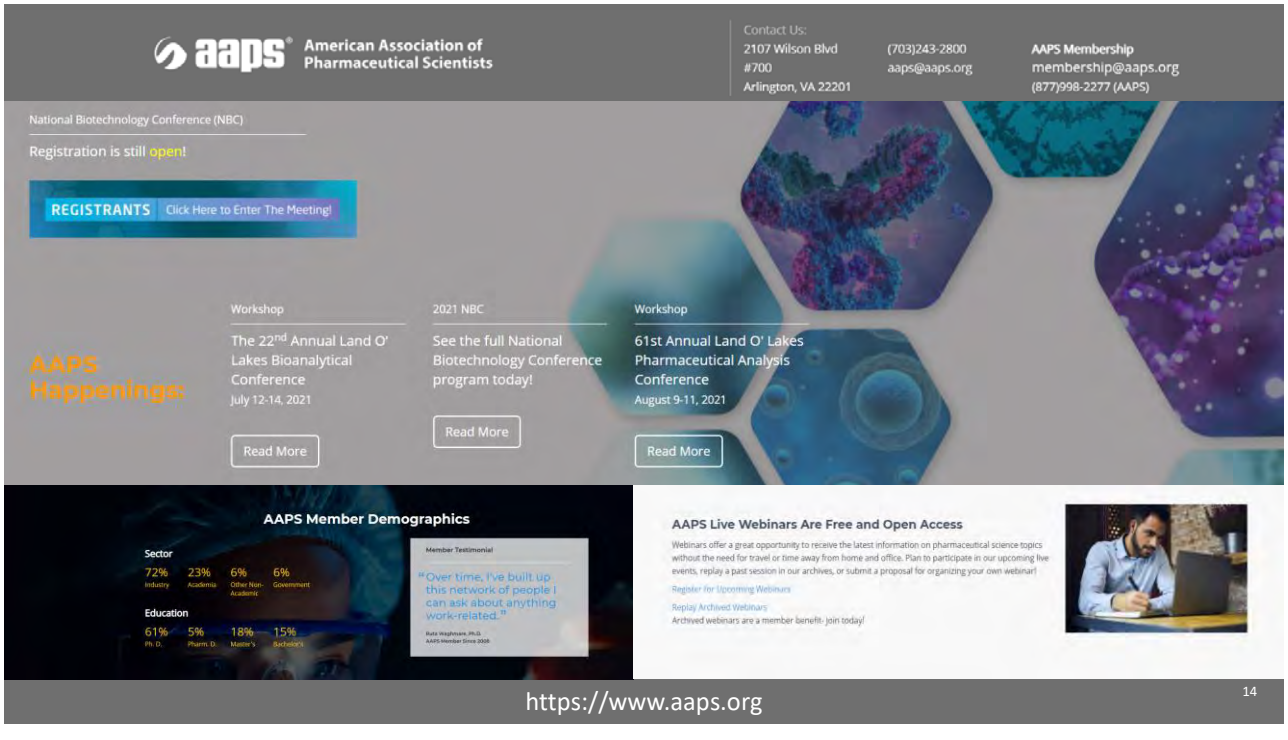

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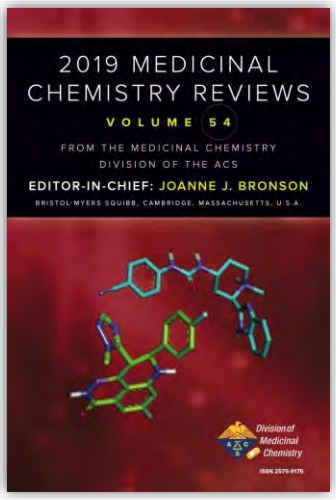

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COVID-19 Vaccines Update: Emerging Questions & Future Applications
Dr. Shane Crotty and Dr. Yizhou Dong offer their insights on the progress of COVID-19 vaccine research including the potential for future applications to other diseases and therapeutics.

The Discovery of Sotorasib (AMG 510): First-in-Class Investigational Covalent Inhibitor of KRAS G12C
Brian Lanman of Amgen outlines the strategies used to overcome these challenges of KRAS, one of the most frequently mutated oncogenes in human cancer.

An Integrated Approach: Oral Delivery of a Fatty Acid Acylated GLP-1 Peptide
Stephen Buckley of Novo Nordisk shares how this coformulation provides a unique, site-directed release and absorption in the stomach and effectively surmounts inherent challenges relating to solubility, molecular size, and proteolytic lability to achieve therapeutically relevant plasma exposure of semaglutide.

Online vs. In-Person: Networking as a Medicinal Chemist
With the suspension of in-person meetings due to the coronavirus pandemic, scientists need to shift to networking virtually in order to remain connected. Join our panel as they share how to make the most out of virtual networking opportunities.

How Computational Chemistry is Accelerating Drug Discovery
Scott Edmondson, the Sr. Vice President and Head of Chemistry at Nimbus Therapeutics, discusses how SBDD is leveraged to deliver clinical candidates that are differentiated from others in their class by their exquisite selectivity.

Targeted Delivery of RNA-targeted Therapeutics
Punit Seth of Ionis Pharmaceuticals discusses examples of different strategies for delivery of oligonucleotide drugs. Learn about the recent advances in receptor-mediated delivery which have greatly expanded the repertoire of cell-types and tissues that are now accessible for antisense drug-discovery.

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Service Dogs in Your Chemistry Lab

Date: Wednesday, September 22, 2021 @ 2-3pm ET
Speakers: Patricia Redden, Saint Peter's University / Joey Ramp, Empower Ability Consulting, LLC / Ashley Neybert, Independence Science
Moderator: Partha Basu, Indiana University-Purdue University Indianapolis

Register for Free!

What You Will Learn:

- What does the Americans with Disabilities Act cover regarding access rights for service dogs
- How is a service dog selected for certain jobs or disabilities, and what type of training is required
- What types of service dogs exist and what is the process to obtain one

Co-produced with: Chemists with Disabilities (CWD) Committee, ACS Department of Diversity Programs, and ACS Diversity, Inclusion & Respect Advisory Board

Molecules to Manufacturing to Marketplace

3D Printing of Sulfonated Polyesters for Controlled Release

Date: Thursday, September 23, 2021 @ 2-3:15pm ET
Speakers: Timothy Long, Arizona State University and Michael Bortner, Virginia Tech
Moderator: Bryan Tweedy, American Chemical Society

Register for Free!

What You Will Learn:

- What is the impact of polyester ionomers and macromolecular architecture on processability and performance of 3D printed structures
- How to leverage rheology for predictive additive manufacturing system design and materials screening
- A snapshot of the topics and concepts captured in the ACS Polymer Chemistry: Principles and Practice short course held at Virginia Tech

Co-produced with: ACS Professional Education

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A TRAVÉS DEL PRISMA DE LA CROMATOGRAFÍA

Fecha: Miércoles, 29 de Septiembre @ 2-3pm ET (1-2pm CT)
Ponente: Elena Stashenko, Universidad Industrial de Santander
Moderadora: Ingrid Montes, Universidad de Puerto Rico, Recinto de Río Piedras y American Chemical Society

Registrarse Gratuitamente

Lo Que El Público Aprenderá:

- Junto con la biodiversidad biológica existe una diversidad molecular bastante amplia para cuyo estudio son indispensables las técnicas de cromatografía y espectrometría de masas
- Los llamados metabolitos secundarios desempeñan papeles importantes para la comunicación, la adaptación, y la supervivencia de las plantas
- El color de algunas flores está asociado con la capacidad antioxidante de sus colorantes

Co-producido con: Sociedad Química de México y *Chemical & Engineering News*

This collaboration with the Mexican Society of Chemists will be in Spanish.

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Designing Around Structural Alerts in Drug Discovery

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Designing around Structural Alerts in Drug Discovery

NICK MEANWELL
Vice President, Research and Early Development, Bristol-Myers Squibb

DEEPAK DALVIE
Vice President, Drug Metabolism and Pharmacokinetics, Crinetics Pharmaceuticals

Presentation slides available now! Today's recording will be made available to all registrants for 24 hours before moving to www.acs.org/acswebinars as an exclusive member benefit.

This ACS Webinar is co-produced with the ACS Division of Medicinal Chemistry, American Association of Pharmaceutical Scientists, and ACS Publications.

Outline

- **The problem:**
  - adverse drug reactions and manifestations of toxicity
  - drug withdrawals, BBWs and rejections due to liver toxicity
- **Drug-induced liver disease – DILI**
  - underlying mechanisms
- **Metabolic activation of drugs and toxicity**
  - background studies that attempt to provided perspective
  - assessing reactive metabolite formation and covalent binding to proteins
- **A synopsis of structural alerts**
  - problematic functionality and the underlying mechanistic organic chemistry
- **Approaches to mitigating reactive metabolite problems**
  - strategies and tactics
- **Conclusion**

A. Kalgutkar, *J. Med. Chem.* 2020, **63**, 6276−6302

Bristol Myers Squibb

ADVERSE DRUG REACTIONS AND WITHDRAWALS

The Role of Metabolic Activation

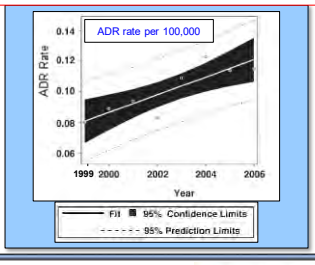
Adverse Drug Reactions (ADRs)

- ADRs were estimated to be the **4th leading cause of death** in the US in **1994**
  - deaths estimated at 106,900 (95% CI 76,000-137,000)
  - ADR death rates increased between 1999 and 2006
  - over 2 million serious ADRs per year: $136 billion yearly cost
- ADRs have been divided into 5 categories
  - Type A accounts for 80%
  - Type B has an underlying chemical basis

Type	Description	Underlying Effect	Examples
A	Augmented Reactions	Dose-related extension of pharmacology	Excessive hypotension with antihypertensive agents; rhabdomyolysis with statins
B	Bizarre Reactions	Idiosyncratic – immune or non-immune mediated Rare: 1 in 10-50,000	Troglitazone and tienilic acid hepatotoxicity
C	Chemical Reactions	Dose-related; molecular understanding	Acetaminophen, isoniazid hepatotoxicity
D	Delayed Reactions	Occur after many years of drug ingestion	Teratogenicity after drug intake during pregnancy - thalidomide
E	End-of-treatment Reactions	Adverse reactions on drug withdrawal	Withdrawal seizures after stopping phenytoin

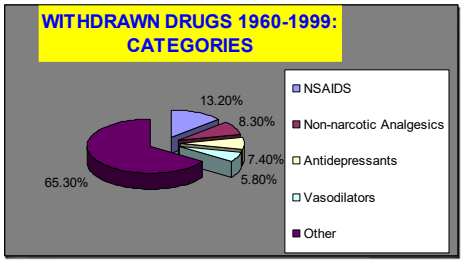
Disease	Per annum
Heart disease	743,460
Cancer	529,904
Stroke	150,108
ADRs	106,900
Pulmonary Disease	101,077
Accidents	90,523
Pneumonia	75,719
Diabetes	53,894

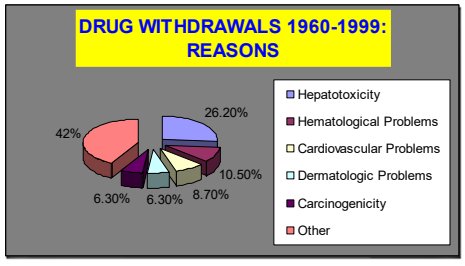
ADR death rates increased between 1999 and 2006



B. K. Park *et al*, *Chem. Res. Toxicol.*, 1998, **11**, 969-988; J. Lazarou *et al.*, *JAMA*, 1998, **279**, 1200-1205; G. Shepherd *et al.*, *Ann. Pharmacother.*, 2012, **46**, 169-175
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm

Withdrawals of Prescription Drugs 1960-1999



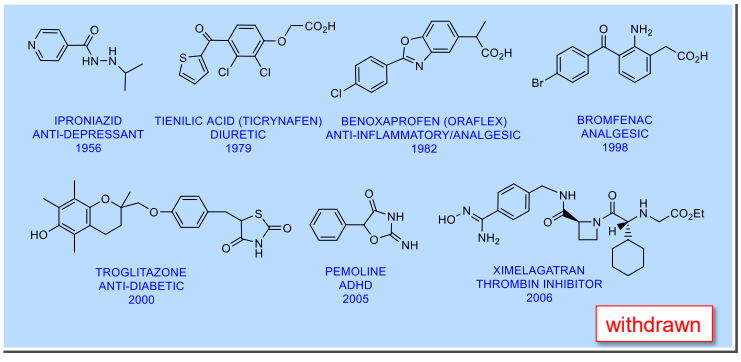


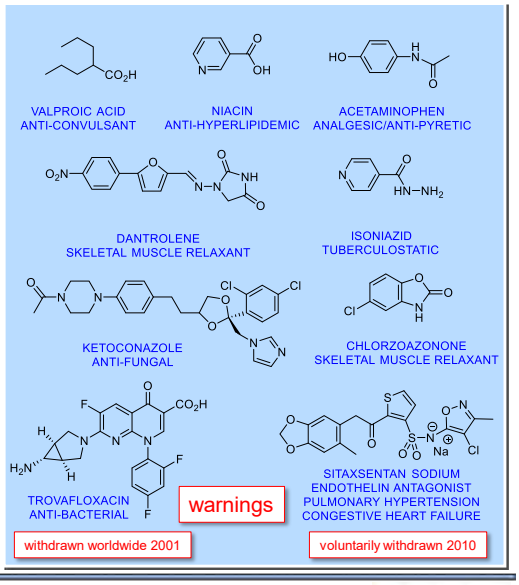
- 121 Drugs withdrawn from world markets 1960-1999 for safety reasons
- NSAIDs most common category associated with drug withdrawal
- Many of the antidepressants withdrawn are MAO inhibitors
- Hepatotoxicity is the leading cause of drug withdrawal

"Hepatotoxicity is the most common adverse effect causing major drug problems including withdrawals and refusal to approve"
Dr Robert Temple (FDA): Drug-Induced Liver Injury: A National and Global Problem, Feb. 12-13th, 2001, *Westfields Conference Center*, Chantilly, VA

Man Fung *et al.*, *Drug Information Journal*, 2001, **35**, 293-317

Drugs With Liver Toxicity Problems

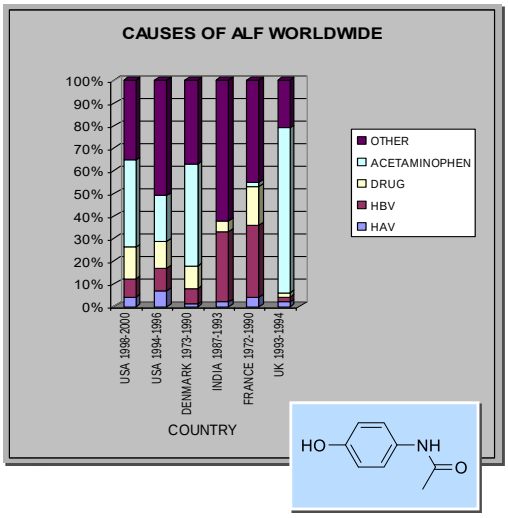




- **Structurally disparate and mechanistically diverse**
- **Reactive metabolites suspected and examined in several cases**
  - iproniazid, tienilic acid, troglitazone
  - sitaxsentan and trovafloxacin ultimately withdrawn by Pfizer
- **Sitaxsentan and trovafloxacin ultimately withdrawn by Pfizer after warning labels added**
- **Difficult to establish definitive cause and effect relationship**
  - no evidence that ximelgatran is associated with reactive metabolites
  - immune mediated: human leukocyte antigen (HLA) - HLA-*DRB1*07*

Drug-Induced Liver Injury (DILI)

- **Most instances of DILI are idiosyncratic in nature**
  - no reliable biomarkers
  - focus on reactive metabolites: retrospective studies
- **Mitochondrial toxicity is an uncommon but distinctive form of liver toxicity**
  - tetracycline, amiodarone, valproic acid
  - problem with HIV-1, HBV nucleoside analogues: inhibition of host DNA pol γ
- **Cholestatic DILI - transporter involvement**
  - bile salt export pump (BSEP, ABCB11): cyclosporin, rifampicin
  - multi-drug resistance-associated protein 2 (MRP2, ABCC2)
  - multi-drug resistance protein 3 (MDR3)
    - these transporters are genetically polymorphic proteins
- **Immune mechanisms of DILI**
  - antibodies to liver proteins: hapten hypothesis - tienilic acid
  - human leukocyte antigen (HLA) allele binding

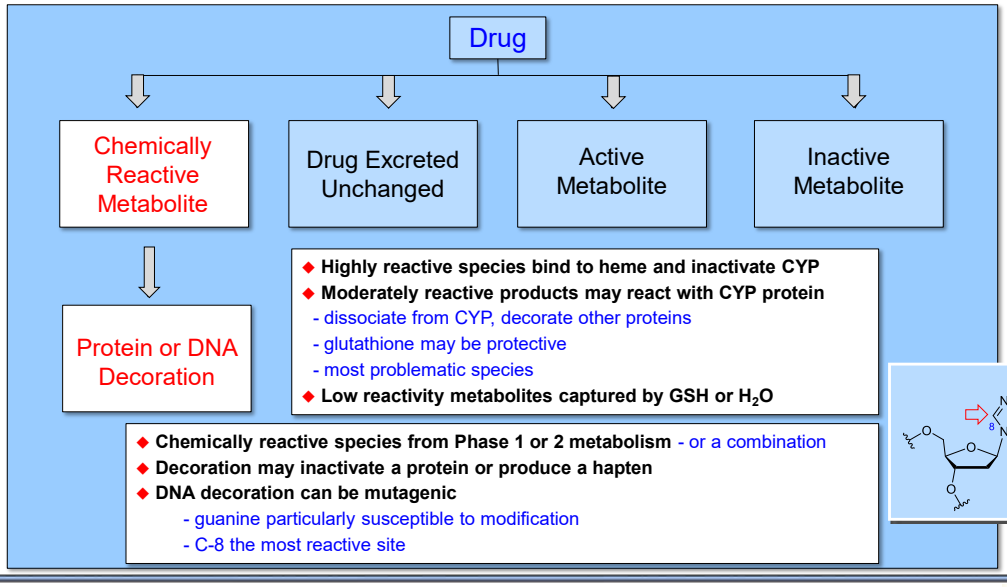


S. Tujios and R.J. Fontana, *Nature Rev. Gastroenterol. Hepatol.*, 2011, **8**, 202-211; W. Lee, *Hepatology*, 2007, **46**, 966-970
W. Lee, www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm122459.pdf ; G. Ostapowicz *et al., Ann. Intern. Med.*, 2002, **137**, 947-954

METABOLIC BIOACTIVATION

In Vitro Techniques and Metabolic Pathways

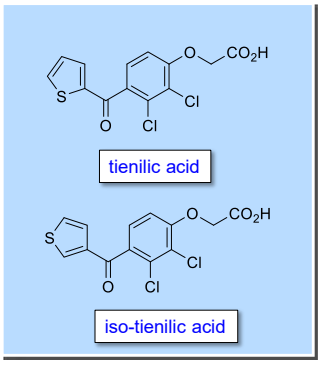
Metabolic Activation and Drug Toxicity

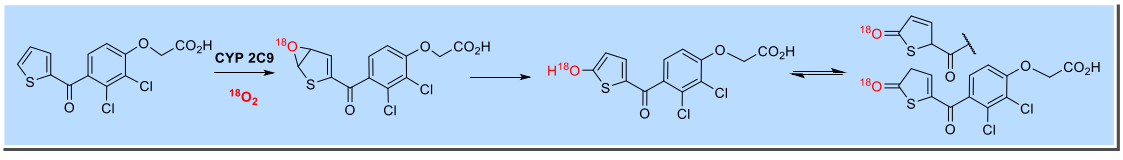


See P.M. Gannet *et al.*, *Org. Biomol. Chem.*, 2018, **16**, 2198-2209 for C-8 guanine modifications & role in cancer

Tienilic Acid (Ticrynafen)

- **Uricosuric diuretic agent introduced in Europe in 1976,**
  - US FDA approval followed in 1979
- **Withdrawn in the US in 1980**
  - severe hepatotoxicity in <1% of patients: 10% fatality rate
- **Drug-induced immunoallergic hepatitis**
  - anti-LKM_2 antibodies detected (liver-kidney microsome)
- **Anti- LKM_2 specifically recognizes CYP 450 2C9**
  - tienilic acid metabolized by CYP 450 2C9
  - covalently binds to a surface residue of 2C9
- **Most compelling example of haptenization hypothesis**
  - thienyl peroxide, thiolactone potential electrophiles
- **Iso-tienilic acid an impurity in early lots of tienilic acid**
  - toxicity profiles of the 2 compounds differ
  - tienilic acid induces immune-mediated hepatitis in humans, not rats
  - iso-tienilic acid directly causes hepatitis in rats
- ***In vitro* metabolic studies comparing tienilic acid & iso-tienilic acid**
  - some illumination of the chemistry underlying the observed toxicity

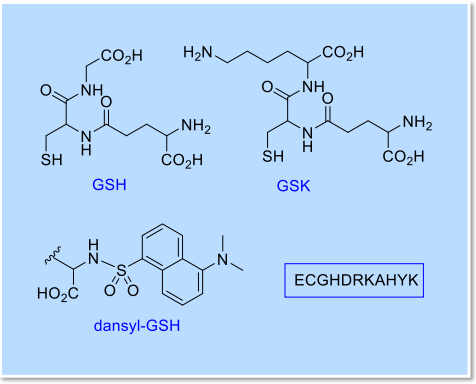




P. Beaune *et al.*, *Proc. Natl. Acad. Sci. USA*, 1987, **84**, 551-555; *Mol. Pharmacol.*, 1996, **50**, 326-333

Assessing Reactive Metabolites

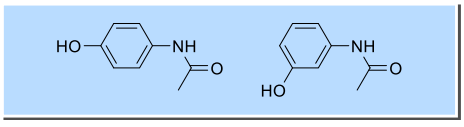
- **Incubate compound with human liver microsomes (HLM)**
- **Analyze for protein covalent binding (PCB) – radio-labeled drug**
- **Evaluate in the presence and absence of glutathione (GSH) or derivative**
  - GSH is a natural protective mechanism
- **Protein binding measured as pmol eq./mg protein**
  - 50 pmol eq./mg protein *in vitro* and *in vivo* suggested as a standard
  - differentiate between propensity to be toxic/non-toxic
- **Analyze for PCB in presence and absence of GSH to assess potential for protection *in vivo***
- **Analyze for (GSH) adducts**
  - can be done with cold drug
  - GSH: soft nucleophile for soft electrophiles
- **Trap with $Na^{14}CN$**
  - CN^- is a hard nucleophile
  - used to trap hard electrophiles like iminium ions



D. Evans *et al.*, *Chem. Res. Toxicol.*, 2004, **17**, 3-16; C. Prakash *et al.*, *Curr. Drug Metab.*, 2008, **9**, 952-964; M.P. Grillo, *Exp. Opin. Drug Metab. Toxicol.*, 2015, **11**, 1281-1302.

Protein Covalent Binding and Toxicity

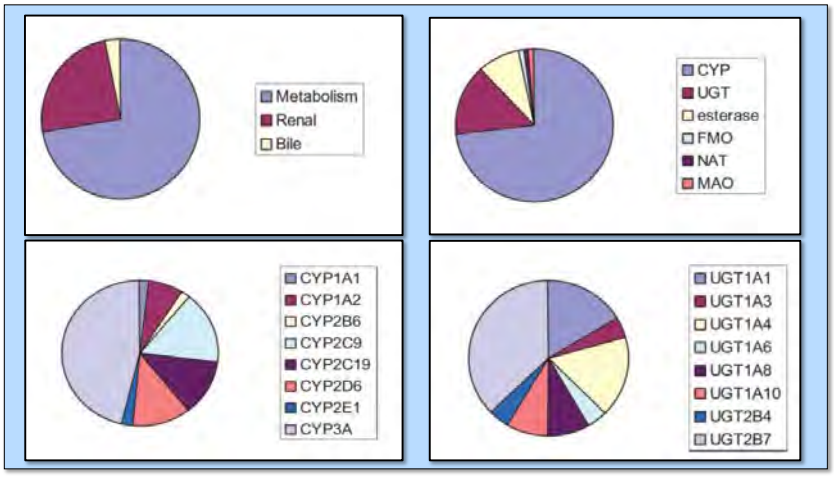
- **Bioactivation/PCB and toxicity correlation not absolute**
  - *meta* isomer of acetaminophen not liver toxic in mice
    - comparable levels of PCB
  - PCB is measure of bioactivation not toxicity
- **PCB *in vitro* in HLM or *in vivo* shows poor correlation for clinically toxic drugs**
  - problematic drugs exhibited higher PCB than safe drugs
  - 1 study separated safe drugs based on dose
- **Necessitates caution in extrapolating PCB to clinical or pre-clinical toxicity**
- **Drugs may be metabolized *in vivo* by different pathways to *in vitro***
  - losartan forms GSH adducts *via* the imidazole moiety *in vitro*
  - metabolism *in vivo*: oxidation of CH_2OH; tetrazole glucuronidation
- **Follow RM assessment in LM with studies in S9 and hepatocytes**
  - understand clearance pathways *in vivo*
  - develop an integrated view of metabolism
- **Clinical indication, drug dose are additional factors that provide context**
  - low dose drugs less likely to cause idiosyncratic toxicity

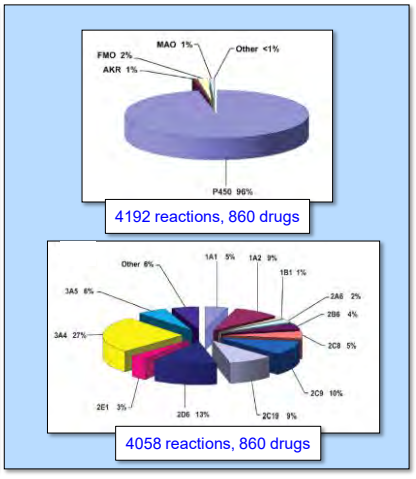


H. Takakusa *et al.*, *Drug Metab. Disp.*, 2008, **36**, 1770-1779; R.S. Obach *et al.*, *Chem. Res. Toxicol.*, 2008, **21**, 1814-1822; T. Usui *et al.*, *Drug Metab. Disp.*, 2009, **37**, 2383-2392
W. Lee, *www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm122459.pdf*; G. Ostapowicz *et al.*, *Ann. Intern. Med.*, 2002, **137**, 947-954; W. Lee, *Hepatology*, 2007, **46**, 966-970

Drug Clearance Pathways in Humans

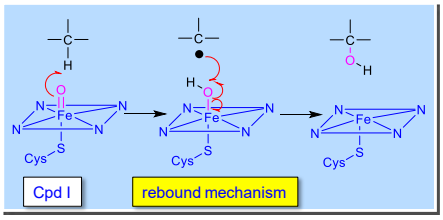
- Clearance mechanisms for the top 200 US drugs in 2002
- CYP-mediated metabolism dominates and CYP 3A4 is the major catalyst
- CYP 450s dominate (>90%)
- 1A2, 2C9, 2C19, 2D6 & 3A4 account for 75%



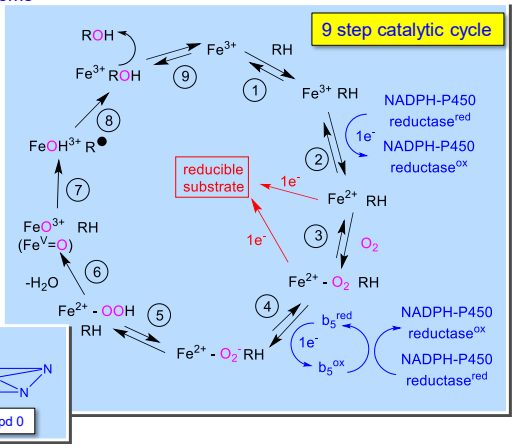


J.A. Williams *et al.*, *Drug Metab. Disp.*, 2004, **32**, 1201-1208; S. Rendic & F.P. Guengerich, *Chem. Res. Toxicol.*, 2015, **28**, 38-42

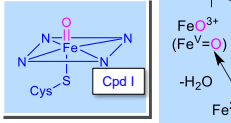
The CYP 450 Catalytic Cycle

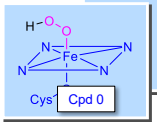


- **Oxidation**
  - CYPs are powerful oxidants
  - Fe=O^{3+} (Fe^{V}=O) the most powerful species
  - rebound mechanism most common pathway for C-H
  - Fe^{2+}-O-O-H can oxidize soft atoms
- **Reduction**
  - CYPs can act as reducing agents
  - occurs with some substrates when binding of O_2 is slow



- **Oxidation cycle is initiated by substrate binding**
  - Fe^{3+} (ferric) is reduced to Fe^{2+} (ferrous) by e$^-$ transfer from NADPH
  - Fe^{2+} species binds O_2
- **Fe^{2+}-O_2 complex is a reducing agent whilst waiting for an electron**
  - the single electron can be transferred to the substrate
  - facilitated by some substrates blocking O_2 binding
  - can reduce N-O, N-N bonds, C-halogen bonds
- **Fe^{2+}-O-O-H is an oxidant and a nucleophile** (Cpd 0)
  - sulfur, anilines (CYP 1A2), soft atoms
  - may hydrolyze nitriles (Fe^{2+}-O-O$^-$)
- **Fe^{2+} (ferrous) is readily oxidized to Fe^{3+} (ferric)**
- **Fe=O^{3+} (can be written as Fe^{V}=O) is the major oxidizing species** (Cpd I)
  - capable of a broad repertoire of reactions



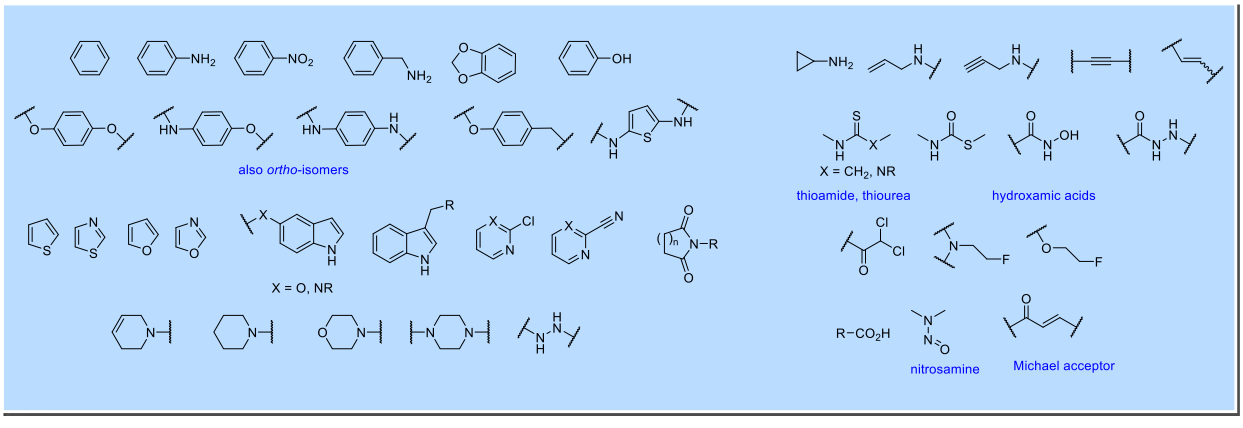


F.P. Guengerich, *Chem. Res. Toxicol.*, 2001, **14**, 611-650; *J. Biol. Chem.*, 2013, **288**, 17065-17073; *Trends Pharmacol. Sci.*, 2016, **37**, 625-640
S. Shaik *et al.*, *Acc. Chem. Res.*, 2019, **52**, 389-399

A SYNOPSIS OF STRUCTURAL ALERTS

And The Underlying
Mechanistic Organic Chemistry

Structural Alerts

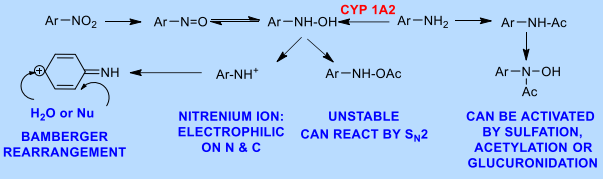


- **Phenyl rings feature prominently**
  - may reflect ubiquity in drug design
  - most common ring in marketed drugs
- **Common functionalities can be problematic**
  - carboxylic acids
  - olefins

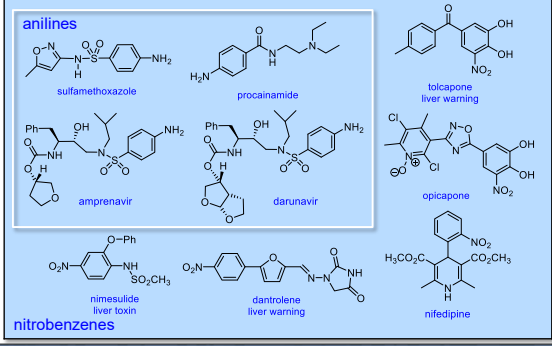
Structural Alerts – a Survey of Toxicophores

Anilines & Masked Anilines
Darunavir, Dapsone, Procainamide

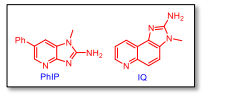
Nitrobenzenes
Nifedipine, Dantrolene, Tolcapone, Flutamide

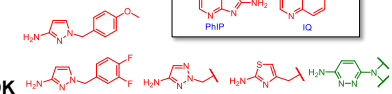


Marketed drugs



- **3 factors identified as contributing to aniline mutagenicity:**
  - F1: facility of the aniline binding to CYP 1A2 active site
  - F2: ease of proton abstraction from $ArNH_2$
  - F3: susceptibility of ArNH-OH bond to H^+-mediated heterolysis
- **The 3 factors operate strictly in a sequential fashion**
  - order of importance: F1>F2>F3
  - disruption of 1 factor will make the subsequent steps irrelevant
- **Applies to *some* heterocycles**
  - food-derived mutagens PhIP
  - amino pyrazoles,
  - amino triazoles
  - amino thiazoles
- **Amino pyridazines OK**

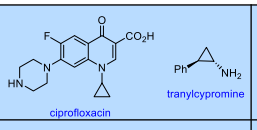


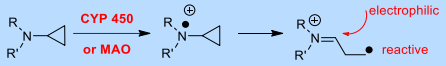


I. Shamovsky *et al.*, *JACS*, 2011, **133**, 16168-16185; N.J. Gooderham *et al.*, *Drug Metab. Disp.*, 2001, **29**, 529-534
O. Bezençon *et al.*, *J. Med. Chem.*, 2017, **60**, 9769-9789; J.J. Crawford *et al.*, *Chem. Res. Toxicol.*, 2020, **33**, 1950-1959

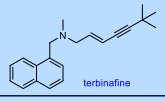
Structural Alerts – a Survey of Toxicophores

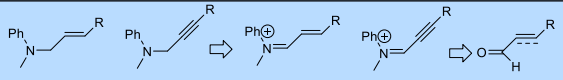
Cyclopropylamines
Ciprofloxacin, Nevirapine, Tranylcypromine, Abacavir



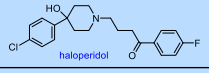


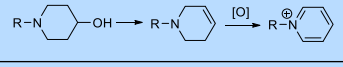
Allylic Amines
Terbinafine



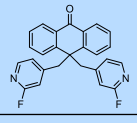


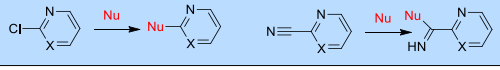
1,2,3,6-Tetrahydopyridines
Haloperidol





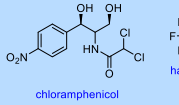
2-Halo- and 2-Cyano Pyridines, Pyrimidines
DUP453

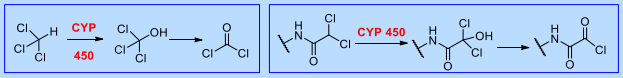




May extend to other leaving groups – e.g. RSO_2, acidic heterocycles

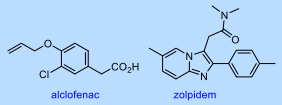
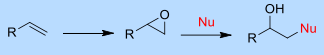
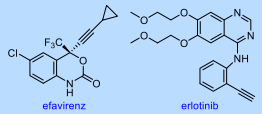
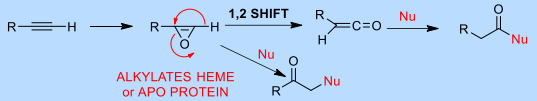
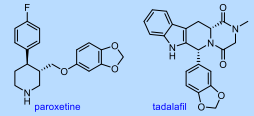
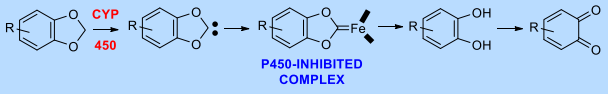
Haloalkanes
Chloramphenicol, Halothane



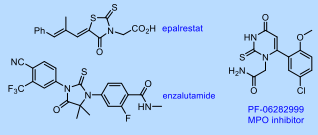
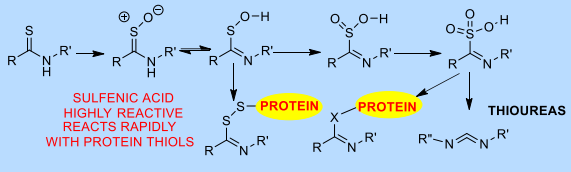
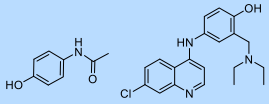
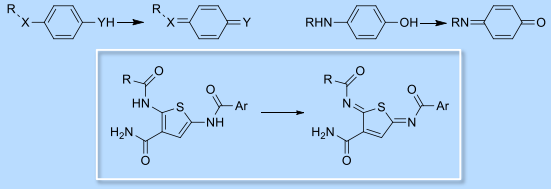
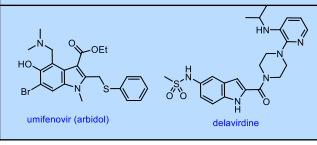
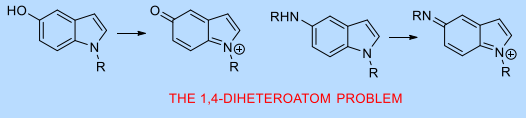


CCl_4 undergoes reductive activation to CCl_3 radical – can react with DNA

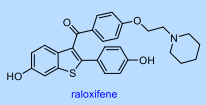
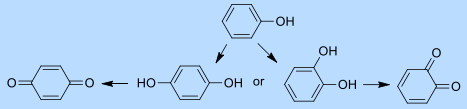
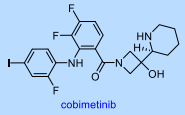
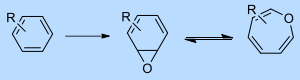
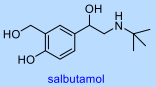
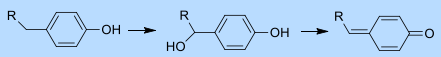
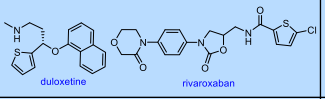
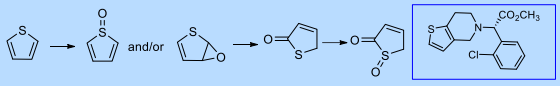
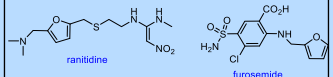
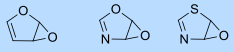
Structural Alerts – a Survey of Toxicophores

Alkenes Alclofenac, Zolpidem		
Acetylenes Efavirenz, Erlotinib, Terbinafine, Selegiline, Rasagiline		
Methylenedioxy Aromatics Paroxetine, Tadalafil		

Structural Alerts – a Survey of Toxicophores

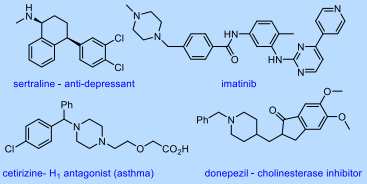
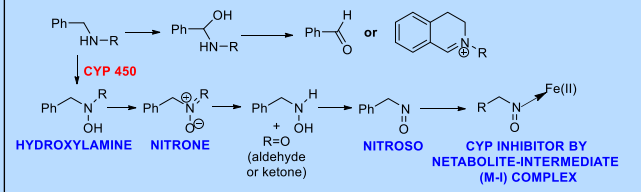
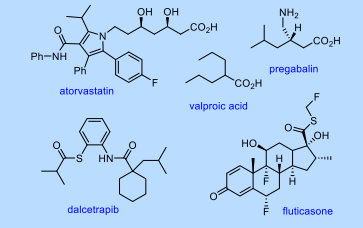
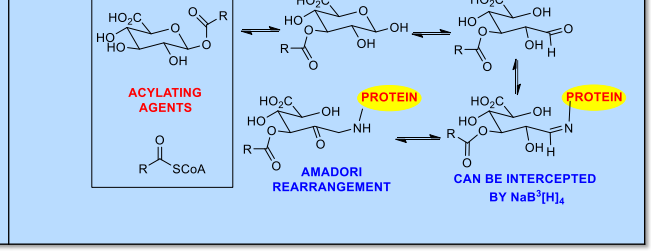
Thioureas, Thioamides Ethionamide, Methimizole, Quazepam, Epalrestat, Enzalutamide, PF-06282999		
1,4-Hetero-Substituted Aromatics Acetaminophen, Amodiaquine extends to thiophenes		
5-OH, OMe or Amino Indoles Umifenovir, Delavirdine		

Structural Alerts – a Survey of Toxicophores

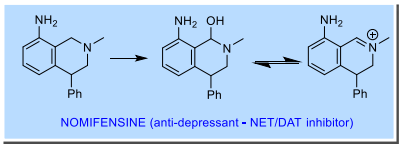
Phenols, Hydroquinones Raloxifene		
Benzene, Bromo- & Iodo benzenes Cobimetinib		
Substituted Toluenes Salbutamol		
Thiophenes Duloxetine, Olanzapine, Tiotropium; Rivaroxaban, Clopidogrel		
Furans, Oxazoles, Thiazoles Ranitidine, Prazosin, Furosemide, Dantrolene, Mometasone, Ritonavir		

J.J. Crawford *et al.*, *Chem. Res. Toxicol.*, 2020, **33**, 1950-1959

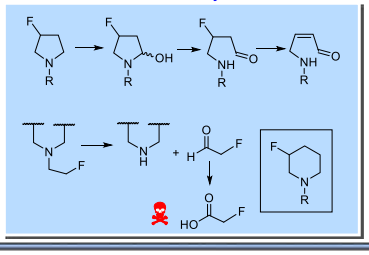
Structural Alerts – a Survey of Toxicophores

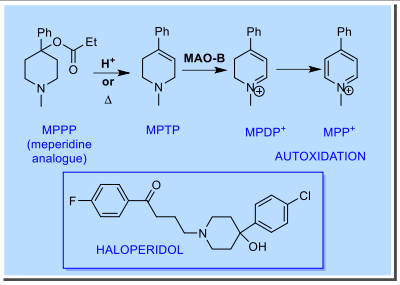
Benzylamines Sertraline, Imatinib, Cetitizine, Donepezil, Cinacalcet		
Carboxylic Acids Valproic Acid, Atorvastatin Pregabalin, Dalcetrapib, Fluticasone (thioesters)		

Amines: Some Special Cases with Concern



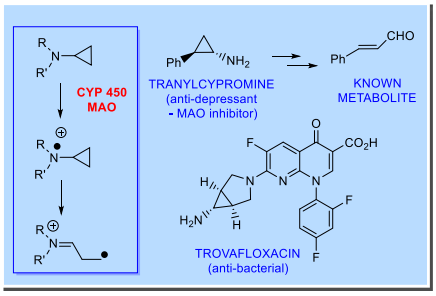
- Cyclic amines
  - α-hydroxylation & H_2O elimination:
  - can lead to cyclic iminium species
  - react with hard electrophiles (CN^-)
  - aldehyde disassociation with acyclic amines
- Nomifensine withdrawn due
  - hemolytic anemia and hepatotoxicity
  - iminium reacts readily with CN^- but not GSH





- Fluorinated amines
  - elimination of HF after α-OH'ation
- Fluoroacetic acid release
  - naturally occurring toxin
  - Krebs cycle: inhibits aconitase
  - lethal doses (mpk):
    - dog: 0.05; rat 0.1-5
    - humans: 2-10

- MPPP causes neurotoxicity
  - haloperidol has similar metabolite



- Cyclopropyl amines undergo ring opening
  - tranylcypromine metabolized to cinnamaldehyde
- Trovafloxacin had BBWs for liver toxicity
  - ultimately withdrawn due to hepatotoxicity

Bristol Myers Squibb

STRATEGIES FOR MITIGATING REACTIVE METABOLITES

Bristol Myers Squibb

Strategies for Reducing Potential Problems

- **Maximize potency, minimize dose**
  - reduces reactive metabolite burden
- **Structural modification**
  - remove or modify problematic structural elements
- **Introduce steric effects**
  - steric shielding of metabolic sites to slow bioactivation
  - reactive metabolites will also likely be subject to steric hindrance
- **Electronic effects**
  - metabolic modification will be kinetically slower, reduced throughput
  - BUT…… metabolic activation produces highly reactive species
  - potential source of problems
- **Introduce a metabolic soft spot**
  - redirects metabolism away from problematic elements
- **Intramolecular capture**
  - proximal nucleophile can capture reactive intermediates

Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

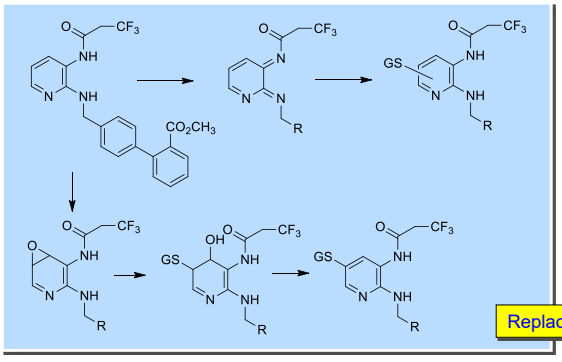
Which of these strategies for reducing potential problems are you familiar with? (Select all that apply)

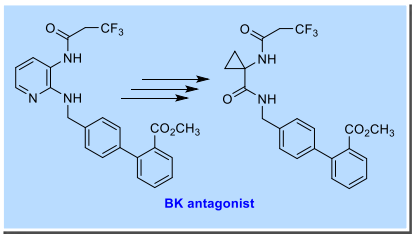
- Structural Modification
- Introduce Steric Effects
- Electronic Effects
- Introduce a Metabolic Soft Spot
- Intramolecular Capture

REACTIVE METABOLITE MITIGATING STRATEGIES

Structural Modification of Problematic Elements

Quinonediimines in Bradykinin Antagonists



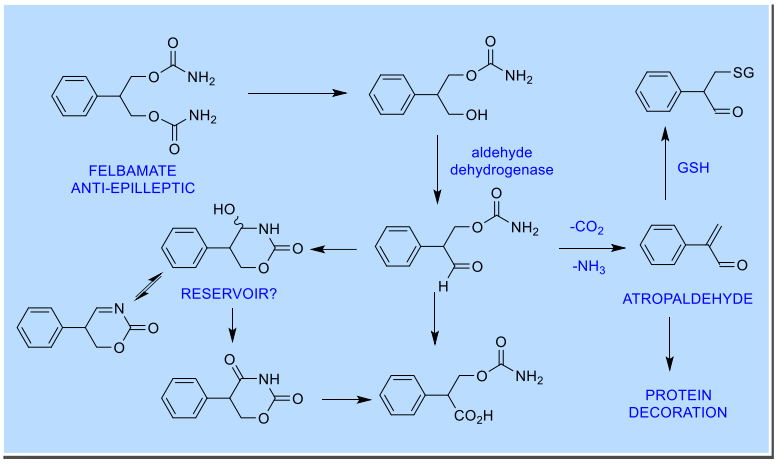


Replace the problematic element

- **Diamino pyridine moiety susceptible to oxidation in bradykinin antagonists**
- **Solution** - isostere of phenylene diamine moiety
  - reduce pyridine moiety to ethylene diamine; add C=O to mimic N
  - dimethyl provides conformational bias - Thorpe-Ingold effect
- **Cyclopropyl optimal – improved topology**
  - electronic overlap with C=O confers additional conformational bias

M.R. Wood *et al.*, *J. Med. Chem.*, 2006, **49**, 1231-1234

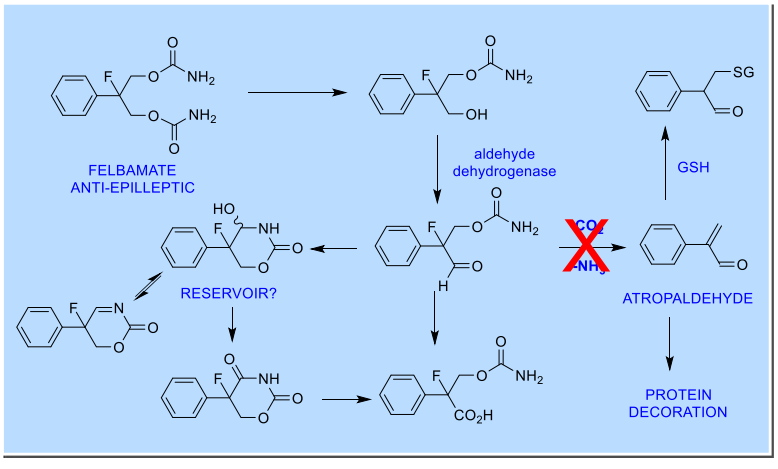
Felbamate Metabolism



- Clinical utility of felbamate limited by aplastic anemia and hepatotoxicity
- Atropaldehyde is potently electrophilic and toxic to fibroblasts
  - thiol adducts found in rat and human urine

C.M. Dieckhaus *et al., Chem. Biol. Interact.*, 2002, **142**, 99-117; 119-134

F-Felbamate Mitigates Metabolic Activation



Block the metabolic pathway

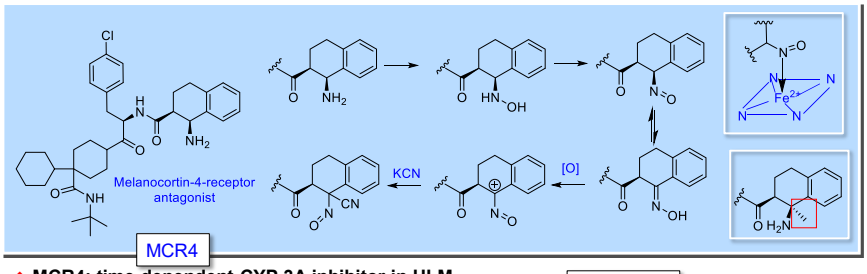
- **Strategic deployment of F based on detailed understanding of metabolism**
- **F atom of fluorofelbamate prevents elimination of carbamate**
  - atropaldehyde not formed

R.J. Parker *et al., Chem. Res. Toxicol.*,., 2005, **18**, 1842-1848

REACTIVE METABOLITE MITIGATING STRATEGIES

Introduce Steric Effects

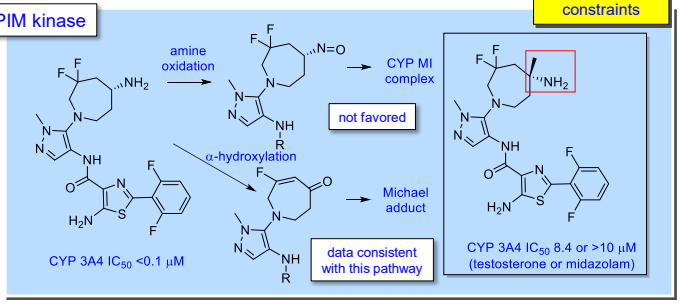
Melanocortin-4-Receptor Antagonist & Pim Kinase



- **MCR4: time-dependent CYP 3A inhibitor in HLM**
  - cyanide adduct identified in HLM containing KCN
- **With rCYP 3A4, saw I_{max} at 450 nM – MI complex**
  - consistent with amine oxidation to nitroso derivative
- **PO administration to rats increased indinavir plasma levels 3x**
  - suggested potential for DDIs in humans
  - development terminated
- **α-CH_3 derivative did not inhibit CYP**
  - steric shielding of amine
  - also blocks metabolic path

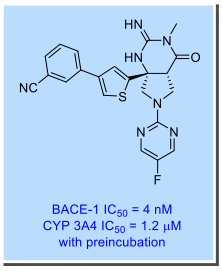
- **PIM kinase: CYP 3A TDI in HLM**
  - met. ID studies implicated azepine
- **Fluorine played critical role in TDI**
  - saw GSH adducts
  - negated nitroso pathway
- **Consistent with Michael acceptor formation**
  - α-hydroxylation to afford C=O
  - elimination of F
  - blocked by α-CH_3

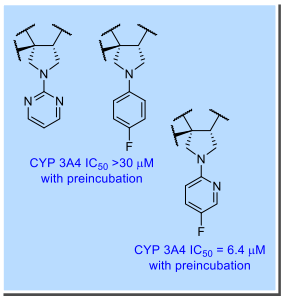
introduce steric/reactivity constraints

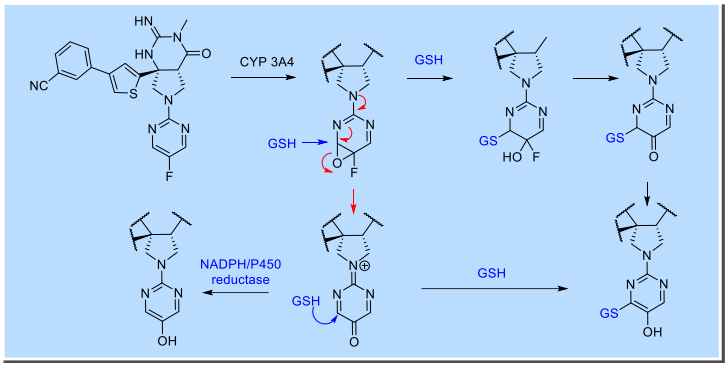


W. Tang *et al.*, *Xenobiotica*, 2008, **38**, 1437-1451; X. Wang *et al.*, *ACS Med. Chem. Lett.*, 2015, **6**, 925-929; B.M. Johnson, N.A. Meanwell *et al.*, *J. Med. Chem.*, 2020, **63**, 6315-6386

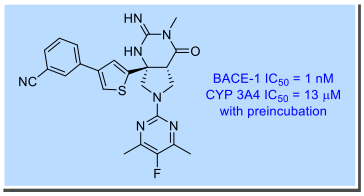
Problems with a Fluorinated Pyrimidine







- **BACE-1 inhibitors**
  - saw time-dependent CYP 450 inhibition
- **Structure-inhibition studies implicated F-pyrimidine**
  - Met ID studies identified minor metabolite of F-pyrimidine
  - +OH, -F
  - with GSH: +OH, -F, + GSH, + 2H
- **Dimethylated pyrimidine reduced CYP 3A4 TDI:** retained BACE-1 inhibition



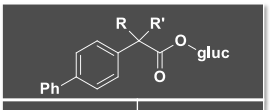
Introduce steric constraints
- slows epoxidation & reaction of imine with GSH

M. Mandal *et al., J. Med. Chem.*, 2018, **61**, 10700-10708

Enhancing Acyl Glucuronide Stability

- **Steric bulk increases AG stability**
- **$t_{1/2}$ of 21 AGs of marketed & withdrawn drugs**
- **Zone classification for predicting toxicity of Ags**
- **$t_{1/2}$: safe drugs ≥7.2 h; unsafe drugs ≤1.7 h**
- **Regression analysis**
  - gave a $t_{1/2}$ of 3.6 h dividing point

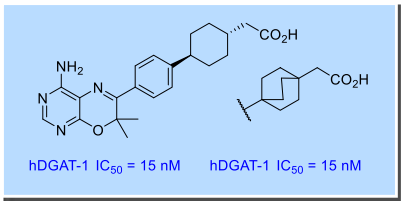
Unsafe	Safe	Dividing Point
$t_{1/2}$ ≤1.7 h	$t_{1/2}$ ≥7.2 h	$t_{1/2}$ = 3.6 h



R, R'	*k* (h^{-1})
H, H	1.07
CH_3, H (*S*)	0.367
CH_3, H (*R*)	0.604
CH_3, CH_3	0.0302
Et, Et	0.00008

Introduce sterically demanding proximal substituents

- **Potent DGAT-1 antagonist**
  - blocks triglyceride synthesis, storage
- **Acyl glucuronide the 1° metabolite**
- **Added bulk to cyclohexane**
  - increases stability of acyl glucuronide
  - $t_{1/2}$ for hydrolysis = 64 h in buffer
  - <15% rearrangement over 80 h

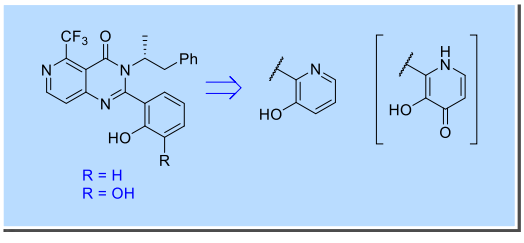


T. Yoshioka *et al., Chem. Res. Toxicol.*, 2009, **22**, 158-172; 1559-1569; 1998-2008; A.M. Birch *et al., J. Med. Chem.*, 2009, **52**, 1558-1568
R. Sawamura *et al., Drug Metab. Disp.*, 2010, **38**, 1857-1864; S.L. Regan *et al., Biopharm Drug Disp.*, 2010, **31**, 367-395

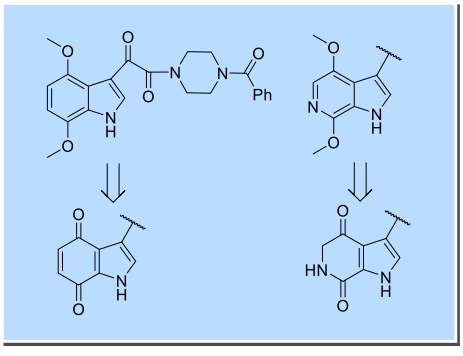
REACTIVE METABOLITE MITIGATING STRATEGIES

Modulate Electronic Properties

Avoiding Quinone-Type Metabolites



Modulate electronic properties



- **Short-acting Ca^{2+}-sensing receptor antagonists for osteoporosis**
- **Lead candidate underwent sequential NADPH-dependent oxidation**
  - gave catechol and *ortho*-quinone in HLM based on GSH trapping
- **Modifying the phenol ring to a pyridine reduced propensity for oxidation**
  - calculations indicated higher oxidation potential
  - 2 F atoms also introduced to the distal phenyl ring
- **56-fold lower GSH adducts with modified molecule**
- **Challenge: maintaining high clearance rate to minimize off-target activities**

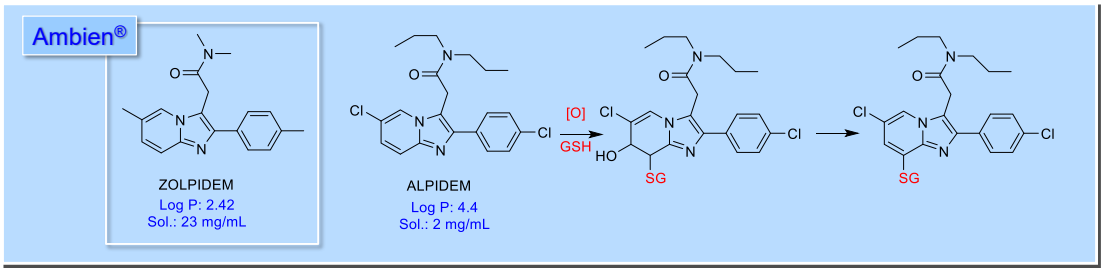
- **HIV-1 attachment inhibitors**
  - demethylation/oxidation to quinone
  - 6-aza would metabolize to amide

A. Kalgutkar *et al.*, *Chem. Res. Toxicol.*, 2010, **23**, 1115-1126; T. Wang *et al.*, *J. Med. Chem.*, 2009, **52**, 7778-7787

REACTIVE METABOLITE MITIGATING STRATEGIES

Introduce a Metabolic Soft Spot or Redirect Metabolism

Olefins in Benzodiazepine Receptor Ligands



- **GABA-chloride channel ligands – ω_1 benzodiazepine receptor**
- **Alpidem – anxiolytic marketed in 1991, withdrawn in 1995 due to liver toxicity**
  - peripheral ω1 – partial agonist – binds to mitochondrial receptor
  - dose: 50 mg TID
  - forms GSH adducts *in vivo* and depletes GSH in hepatocytes
- **Zolpidem – structurally related hypnotic** (Ambien®)
  - 10 mg QD dose
  - central ω1 – full agonist; no peripheral activity
  - no GSH adducts *in vivo* or in hepatocytes
  - metabolic pathways involve oxidation of the two CH_3 moieties
- **Structurally similar but markedly different pharmacology and toxicology**

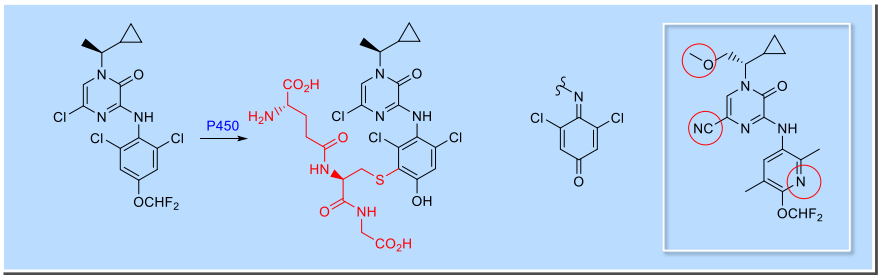
Redirect metabolism

A. Berson *et al., J. Pharmacol. Exp. Ther.*, 2001, **299**, 793-800; A. Durand *et al., Drug Metabolism Rev.*, 1992, **24**, 239-266
D. Garrigou-Gadenne *et al., Drug Metab. Disp.*, 1991, **19**, 574-579, L. Pichard *et al., Drug Metab. Disp.*, 1995, **223**, 1253-1262

REACTIVE METABOLITE MITIGATING STRATEGIES

Combination Approaches

Avoiding Iminoquinone Metabolites in CRF_1



- **Lead identified within a series of potent CRF_1 receptor inhibitors**
  - 60% of dose identified as oxidized metabolites in bile
  - 25% of dose excreted as GSH adducts of phenyl ring
- **Phenyl ring modification focused on pyridine analogue**
  - a survey of pyridyl analogues indicated substantially reduced levels of bioactivation
  - incorporated into molecule selected for further development
- **Pyrazinone ring also subject to bioactivation**
  - required further structural modification to electron deficient CN moiety
- **Major metabolic pathway – *O*-demethylation of alkyl ether introduced as a soft spot**

Combination of approaches – sterics, redirect metabolism

R.A. Hartz *et al.*, *J. Med. Chem.*, 2009, **52**, 7653-7658

CONCLUSION

Conclusion

- **Several functionalities have been associated with problems**
  - in drug discovery & development; post-marketing
  - frequent association with bioactivation
- **Establishing cause-effect toxicity has been difficult in many cases**
  - retrospective search for an understanding of the problem
- **Effect of a particular structural alert can be contextual**
  - many examples of successful drugs that contain potential toxicophores
  - ~50% of small molecule drugs in the top 200 contain structural alerts
- **Metabolism-based toxicity can sometimes be difficult to predict**
  - idiosyncratic toxicity produces low frequency events
  - not always observe in preclinical species
  - utility of drug will depend on severity and availability of alternate therapy
- **Establishing cause-effect toxicity has been difficult in many cases**
  - tienilic acid is the most compelling example
- **Would appear to be prudent to minimize metabolic activation**
  - low dose drugs less frequently associated with problems
  - % metabolized by a particular pathway,
  - alternative pathways of metabolism *in vivo*
  - context of disease for therapy

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Moderadora: Ingrid Montes, Universidad de Puerto Rico, Recinto de Río Piedras y American Chemical Society

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- Los llamados metabolitos secundarios desempeñan papeles importantes para la comunicación, la adaptación, y la supervivencia de las plantas
- El color de algunas flores está asociado con la capacidad antioxidante de sus colorantes

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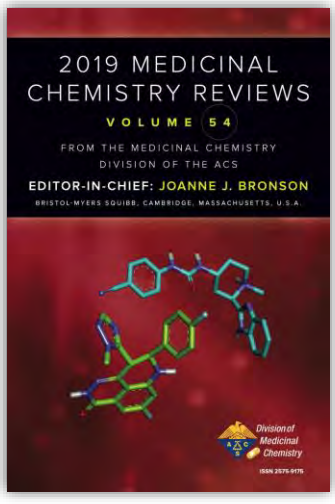

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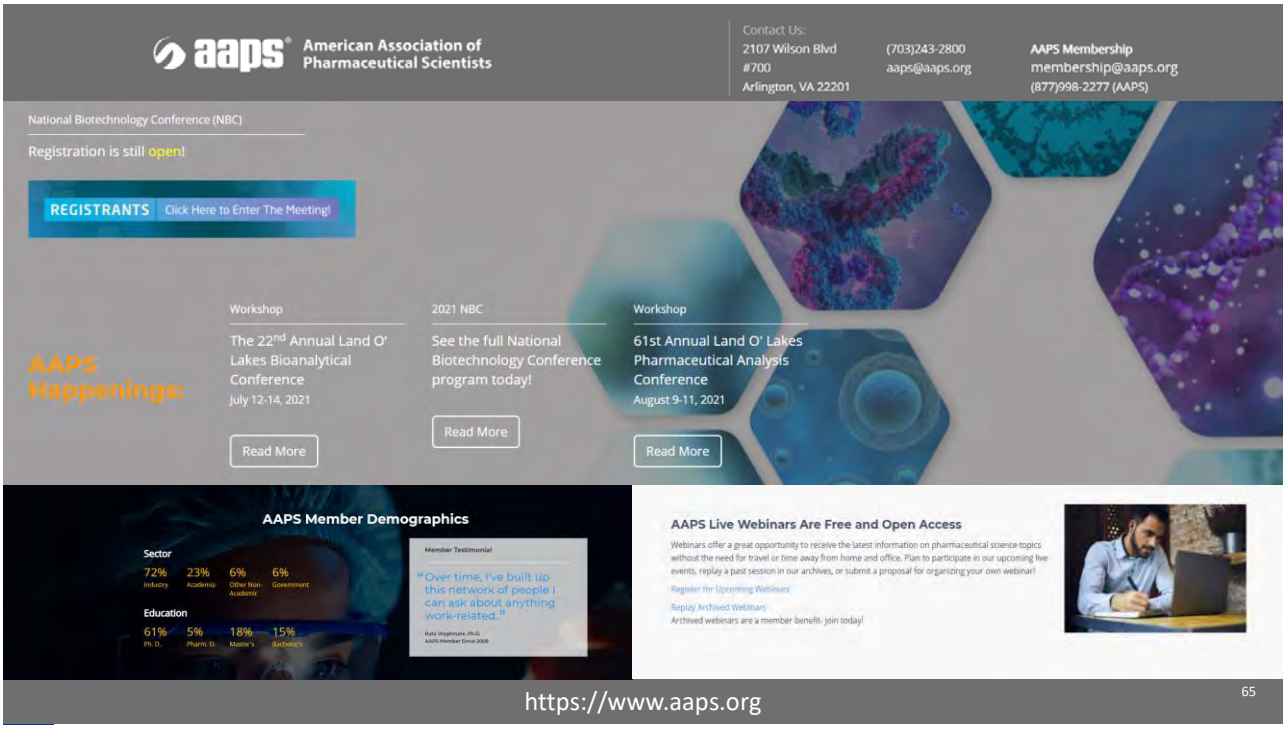

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