PresidX

PresidX Information

PresidX courses
PresidX ADMET database
Structural alerts

Contact : nigel.rogers@btconnect.com

PresidX Courses : 2-day events, run in-house, for 12-45 scientists

PresidX

PresidX 2-day ADMET Course, topics include

- Pharmacokinetics: Clearance, Volume of Distribution, Bioavailability, Mean Residence Time
- Pharmacokinetics and Pharmacodynamics
- Metabolism, Distribution, Excretion
- Absorption, Physicochemical properties and Absorption
- Safety and ADME/PK: drug-drug interactions
- Introduction to Structure and Toxicity
- Receptor-based toxicities: hERG, phospholipidosis, bile salt export pump inhibitors
- Covalent binding and toxicity: Chemistry
- Minor structural changes that modify safety concerns
- *Workshop exercises for individuals and Teams.*

PresidX 2-day Chemical Structure and Safety Course, topics include

- Introduction to Structure and Toxicity
- Toxicities that are not mediated by chemical reactivity
- Receptor-based toxicities: hERG, phosholipidosis, bile salt export pump inhibitors, vasculitis, non-covalent interactions with DNA
- Covalent binding and toxicity: rationale, chemistry, detection, examples
- Phototoxicity
- Genotoxicity
- Minor structural changes that modify safety concerns
- *Workshop exercises for Teams*

PresidX ADMET Data Base : Structure searchable database

[Available on a CD-Rom as an MDL ISIS Desktop v2.5 DataBase file, .dbf (database software not supplied). Can also be supplied as an .sdf file]

PresidX

Description.

- **The latest PresidX ADMET database (v2.0) contains concise descriptions of the Absorption, Distribution, Metabolism, Elimination and Toxicity, ADMET (including Safety Pharmacology) properties of over 1180 compounds together with chemical structure.**
- **Many records include comments on mechanism of action and structure-activity relationships in relation to ADMET, in order to aid improved drug design.**
- **For 170 compounds, selected metabolites or reactive intermediates of interest are illustrated (and structure searchable). Over 600 compounds with ADMET concerns due to reactivity are included.**
- **Learn from information on about 200 compounds withdrawn from the market or discontinued from development and compare with 450 marketed pharmaceuticals**
- **Examples of numbers of compounds with particular properties:**
  - ***adverse effects on liver (>380);***
  - ***blood (>180) ,***
  - ***skin (>50);***
  - ***enzyme inactivators (>120)***
  - ***carcinogenicity (>200)***
  - ***genotoxicity (>200)***
  - ***P-gp inhibitors/substrates (>60)***
  - ***enzyme inducers (>110)***

Data Content:

Molecular Structure: *chemical structure, may contain multiple structures for entries relating to metabolites*
Compound Name: *generic name (or an arbitrary descriptive name based on reference quoted)*
CAS Reg Number: *Chemical Abstract Registration Number (if located)*
Compound Status: *e.g. Marketed (Pharmaceuticals), Withdrawn, Discontinued, Agrochemical, Veterinary Product, Example*
Therapeutic indication: *where appropriate.*
PX_number: *unique PresidX code number*
FW: *formula weight*
Main ADMET Concerns: *uses key words or phrases e.g. liver, blood, inactivator, inducer, carcinogenicity, genotoxic. Inclusion does not imply a safety risk.*
Structure Comment: *key structural features and PX number of the record (if available) that illustrates metabolites.*
ADME Comment: *any special characteristics relating to ADME e.g. species differences, P450 inhibition, metabolic activation, metabolites, enzyme induction.*
Clinical Safety Comment: *focus is on adverse effects, however rare, that may be related to structural features.*
Pre-clinical Safety Comment: *major findings in toxicity studies, including in vitro data.*
Mechanism of Action_ADMET: *possible mechanisms relating to ADMET based on the literature or on comparison with structurally/biologically similar compounds, may be speculative.*
SAR_ADMET: *examples of compounds with similar structures & or ADMET effects.*
Reference _1: *only provided if CAS number not indicated above.*

Designing Safer Compounds: *The Ashby-Tennant supermolecule, structural alerts to DNA reactivity and genotoxic carcinogenicity*

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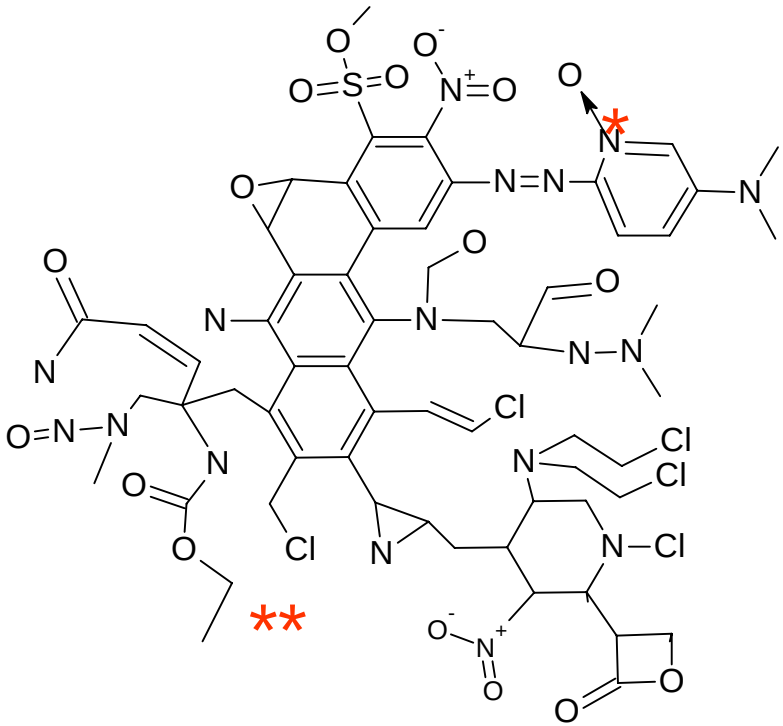

Note

** di-N-oxides such as quinoxaline di-N-oxides appear to be mutagenic, possibly via reduction to reactive radicals but most simple pyridine N-oxides do not appear to be mutagenic*

** * ethyl carbamate is probably mutagenic via 2E1 mediated hydroxylation & formation of vinyl carbamate; most carbamates are not genotoxic unless carbamate facilitates loss of O.*

Refer also to alerts on the FDA web site, www.fda.gov

For database of 1200 examples of compounds with ADMET issues, (> 500 with ADMET issues associated with reactivity) see the structure-searchable PresidX ADMET database, v 2.0

Designing Safer Compounds: *Examples of heterocyclic structures sometimes associated with toxicity or problematic P450 inhibition. Effects depend on substitution pattern, dose, disposition*

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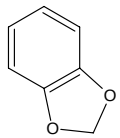
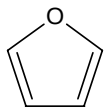
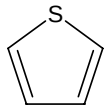
Dioxolanes – P450 MI complex



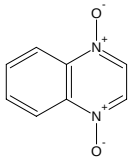


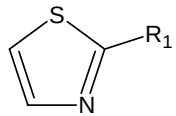
furan – furosemide, ipomeanol
(but prazosin, OK)



thiophene – tienelic acid, ticlopidine
(but olanzapine OK)

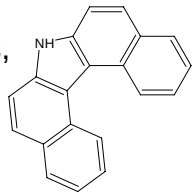
Quinoxaline N-oxides
- carbadox

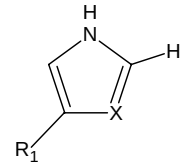




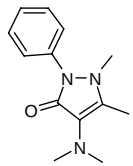
thiazole – thiabendazole or aminothiazole
Possible conversion to thioamides, thioureas (but famotidine OK)

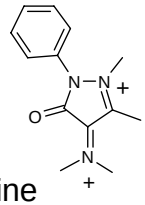
Polyheteroaromatics, often 1A substrates – example shown





e.g. P450 inhibition, thiazole – ritonavir
imidazole – cimetidine; also substituted imidazoles – ketoconazole, clotrimazole (but famotidine OK)

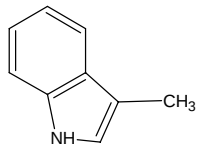




aminopyrine

easily oxidisable heterocycles

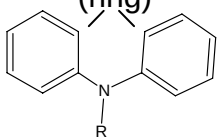
clozapine

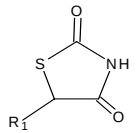


Alkyl substituted indoles, pyrroles
– 3-methylindole

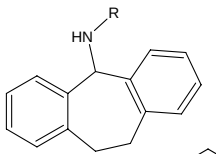
Diphenylamine in ring, e.g. carbamazepine, or not, e.g. diclofenac

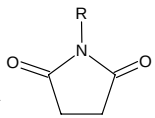
(ring)





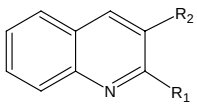
Thiazolidinediones - troglitazone
(but rosiglitazone, pioglitazone OK)

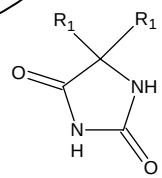




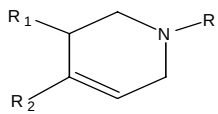
N-phenylsuccinimides – some are nephrotoxic

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





Radical formation – phenytoin
(cf thalidomide)



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

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

Designing Safer Compounds: *Examples of mostly non-heterocyclic structures associated with toxicity or problematic P450 inhibition, most of these alerts relate to reactivity*

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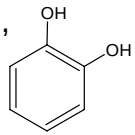
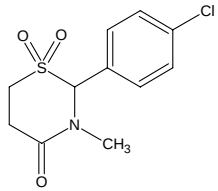
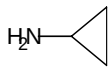
Catechols, Hydroquinones – e.g catechol (but isoproterenol, OK)



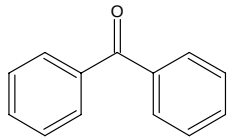
Aldehydes or pro-drugs of, example chlormezanone



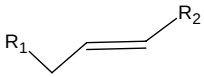
Cyclopropylamine – tranylcypromine, trovafloxacin



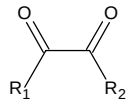
Diaryl ketones – photosensitisers e.g. amiodarone (mebendazole, OK)



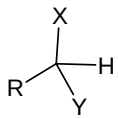
Allyl – tamoxifen, safrole (but droloxifene OK)



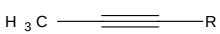
Alpha-diketones – methylglyoxal but hindered examples OK.

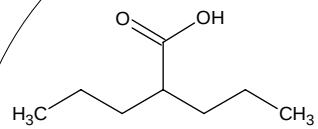


Haloalkanes - halothane

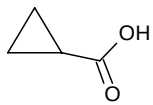


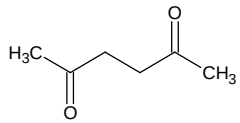
acetylenes – P450 binding & reactive intermediates





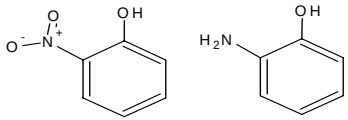
Valproic acid (metabolised to dienoic acid)
Various unusual fatty acids inhibit mitochondrial function
Cyclopropane carboxylic acid

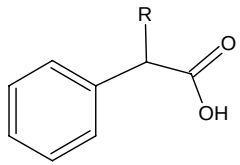




2,5-diketones & related compounds– 2,5-hexanedione

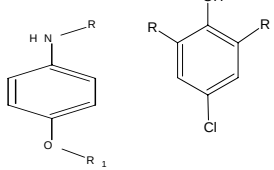
o-amino or nitrophenols – tolcapone (but entacapone OK)

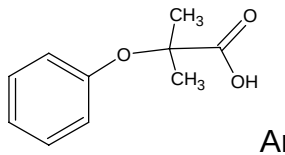




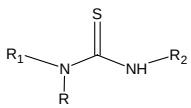
Alkyl propionic & acetic acids – ibufenac, indoprofen (but ibuprofen & many other arylpropionic acids OK)

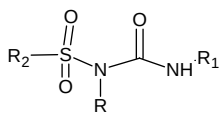
p-aminophenols & ethers-acetaminophen, practolol; some p-chlorophenols – ochratoxin A, PCP & some phenols (but celiprolol, OK)

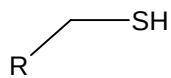




Aryloxy carboxylic acid PPARs (rat specific toxicity)







Thioamides & thioureas - ethionamide, metiamide propylthiouracil

Isocyanate liberating - sulfenofur (note: cf. tolbutamide)

Thiol containing (note captopril, penicillamine marketed)

Designing Safer Compounds: *Examples of alerts to skin sensitisers*

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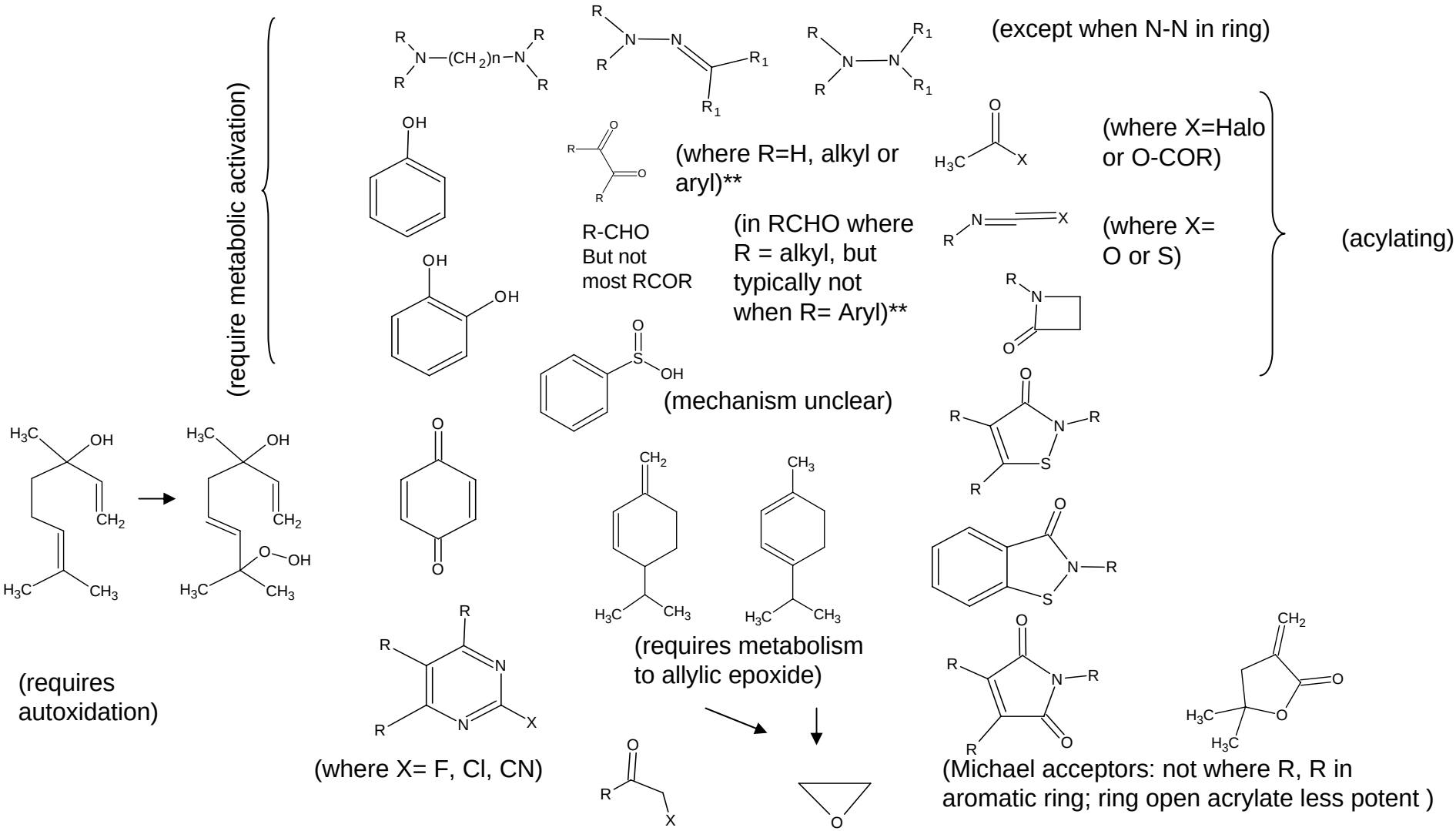

Designing Safer Compounds: *Examples of alerts and example compounds with phototoxicity*

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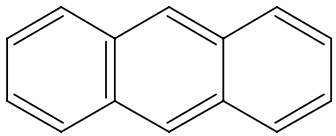
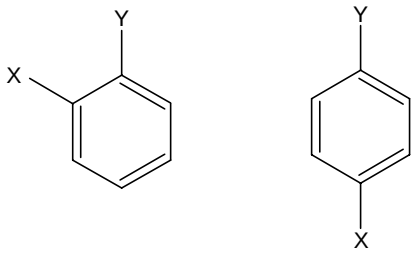
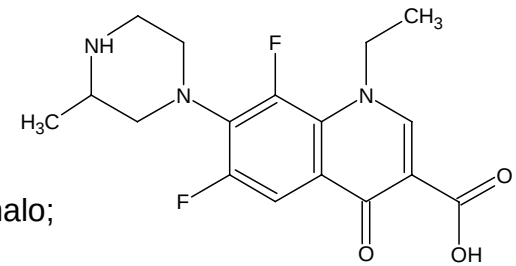
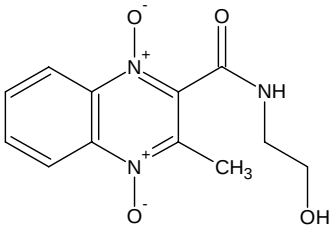


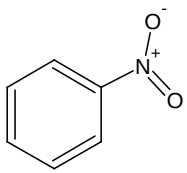
(many polyaromatic hydrocarbons)



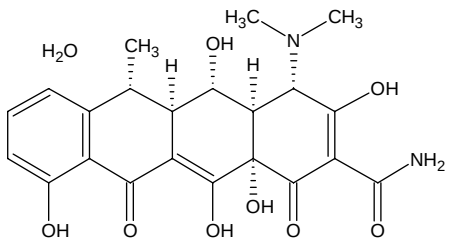
(where Y=N, O, S and X = halo; especially if Y=OH and a salicylanilide; also example where Cl m- to OH)

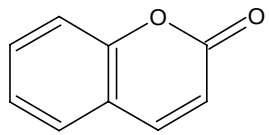


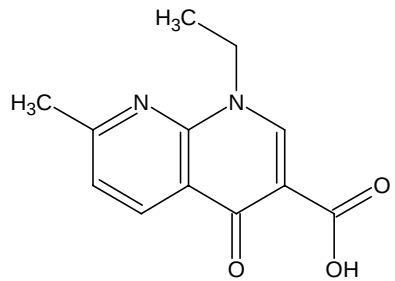


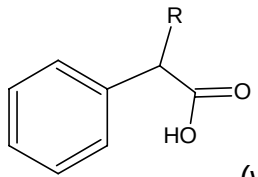


(especially dinitro-)

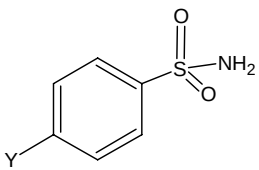








(where R= H or alkyl)



(especially where Y = N)