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RSC Drug Transporters Symposium: Target or Avoid?

Thursday 13th November 2014



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The exploitation and under-exploitation of transporters in drug discovery

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Context



- Member, Nomenclature Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR)
- Editor
 - Senior Editor, British Journal of Pharmacology
 - Transporters are an under-developed therapeutic target. [Discuss](#)
 - 5 Editions of TiPS Receptor and Ion Channel Nomenclature Supplement
 - 5 Editions of BJP Guide to Receptors and Channels
 - The [Concise Guide to PHARMACOLOGY 2013/14](#)
 -[Transporters](#)
 - www.GuidetoPHARMACOLOGY.org



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Plan



- Definitions
- Transporter subfamilies
- Therapeutic targetting of transporters
- Underexploitation?



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Definitions



- Transporter
 - A cell membrane integral protein which allows the movement of solute across the membrane
 - Typically, this movement is against the solute gradient and so requires energy expenditure



Definitions



- Active transporter
 - A transporter which moves solute against the concentration gradient
- Primary active transporter
 - A transporter which exploits the hydrolysis of ATP to allow movement of solute across the membrane
- Secondary active transporter
 - A transporter which exploits the gradient of another solute, usually an inorganic ion, such as sodium or chloride, to allow movement of solute across the membrane
- Facilitative transporter
 - A transporter which allows the passive movement of solute down the concentration gradient



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Definitions



- Substrate
 - A solute which is transported across a cell membrane under the influence of a transporter
 - One fundamental characteristic that defines a substrate is that transport is measurable directly
 - Substrate applied on one side of a membrane can be measured on the other side of the membrane under the influence of the transporter



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Definitions



- Substrate
 - A further characteristic of a substrate is that transport is saturable
 - With increasing concentration of substrate, eventually the capacity of the transporter to convey the substrate across the membrane is reached



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Definitions



- Inhibitor
 - A transporter inhibitor is an agent which itself is NOT transported but which acts to impede the movement of a substrate by a transporter



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Transporter subfamilies



- F- and V-type ATPases
- P-type ATPases
- ATP-binding cassette transporters
- SoLute Carrier transporters
- Other transporters



F-type/V-type ATPases



- Multiprotein complexes (>35 proteins)
- Subcellular organelles
 - F-type
 - Mitochondrial
 - ATP synthesis
 - Driven by proton gradient
 - V-type
 - Lysosomal
 - Generates proton gradient
 - Driven by ATP hydrolysis



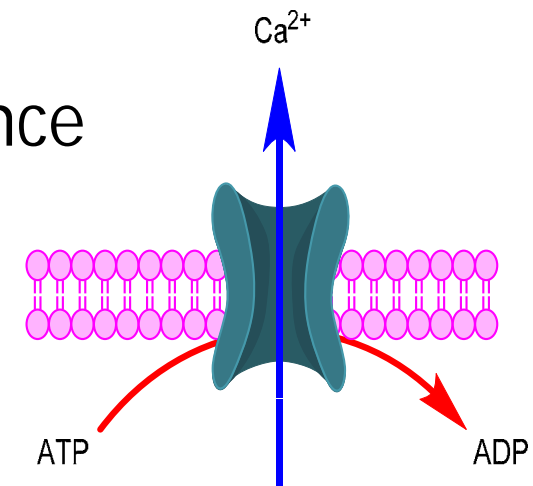
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P-type ATPases



- 34 family members in man in five subfamilies
- Multimeric, often heteromeric
- ATP-dependent ion/phospholipid translocation
- Physiological roles
 - e.g. membrane potential maintenance



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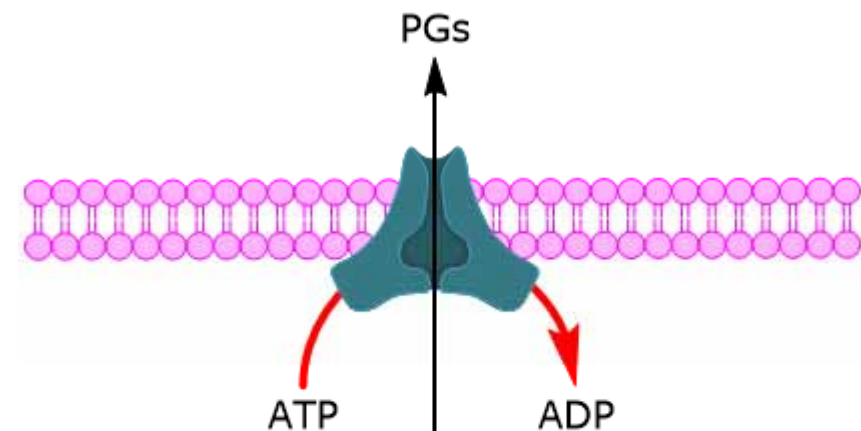
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ABC transporter family



- ~48 family members in man
- Multimeric, mostly homomeric
- ATP-dependent export of solutes out of the cytosol
- Physiological roles
 - e.g. prostanoid export





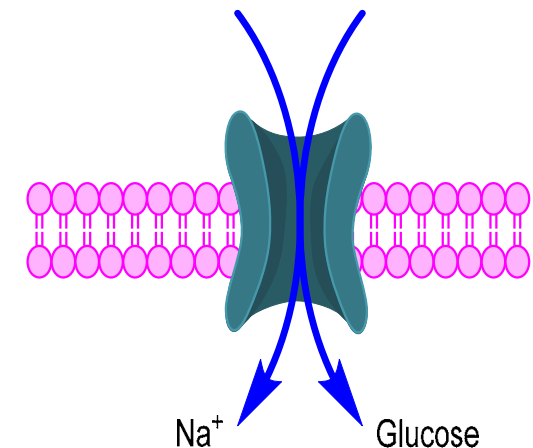
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SLC Solute Carrier Family



- ~400 family members in man
- Multimeric, variable topology & stoichiometry
- Ion-dependent role in solute accumulation
- Physiological roles
 - e.g. glucose transport



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Therapeutic Exploitation

TOADS

Targets Of Approved Drugs



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Approved drugs



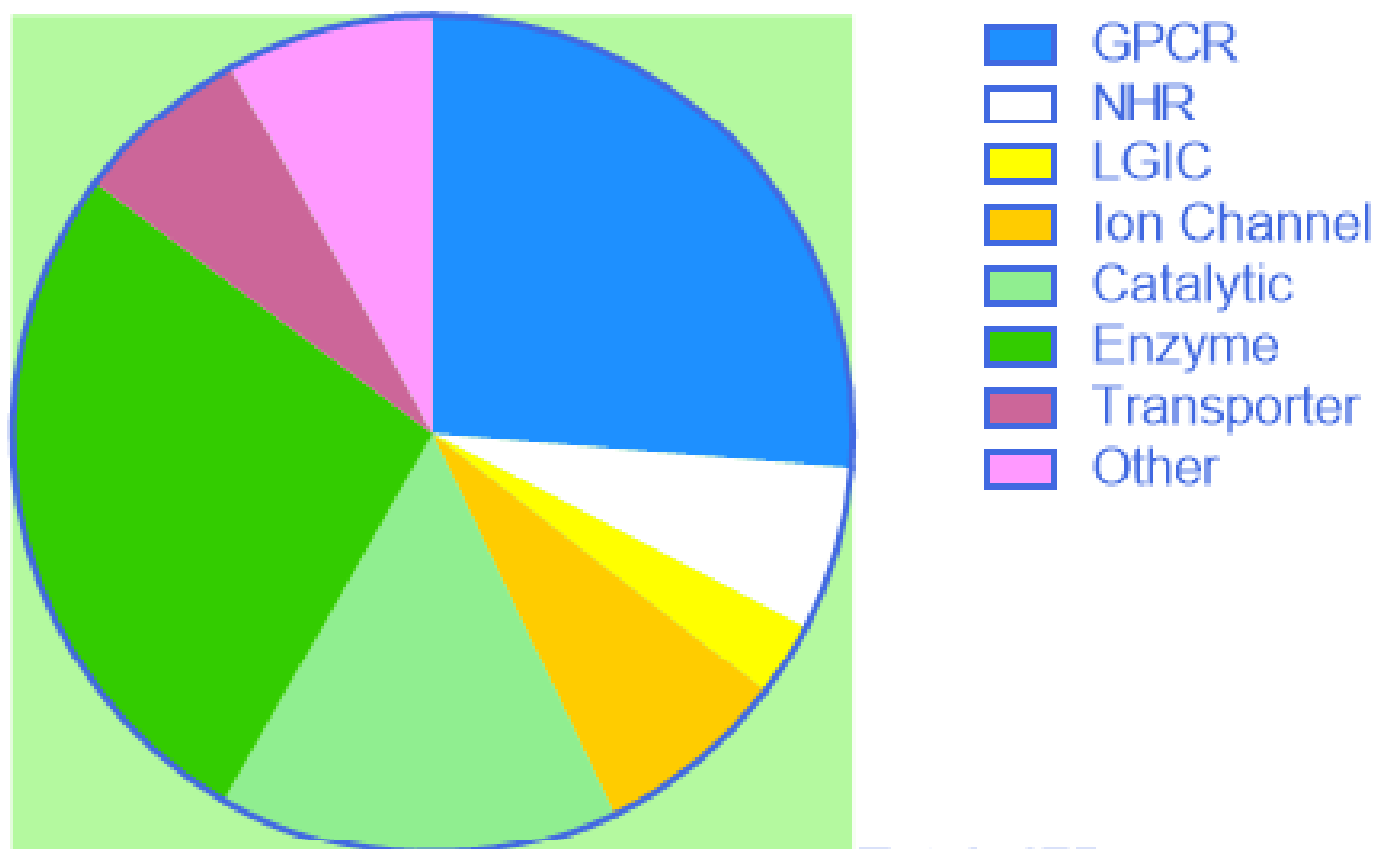
- ~1194 drugs listed in the BNF
 - Anti-infective: 170 (viral, bacterial, parasitic; 14 %).
 - Non-specific: 224 (19 %)
 - Human primary molecular target: 800 (67 %)
 - 251 G protein-coupled receptors;
 - 148 enzymes;
 - 94 nuclear hormone receptors;
 - 59 ion channels;
 - 59 catalytic receptors;
 - 50 no known target;
 - 49 other protein targets;
 - 45 ligand-gated ion channels;
 - 45 transporters;



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Drug Targets in the British National Formulary (2013)



Total=175



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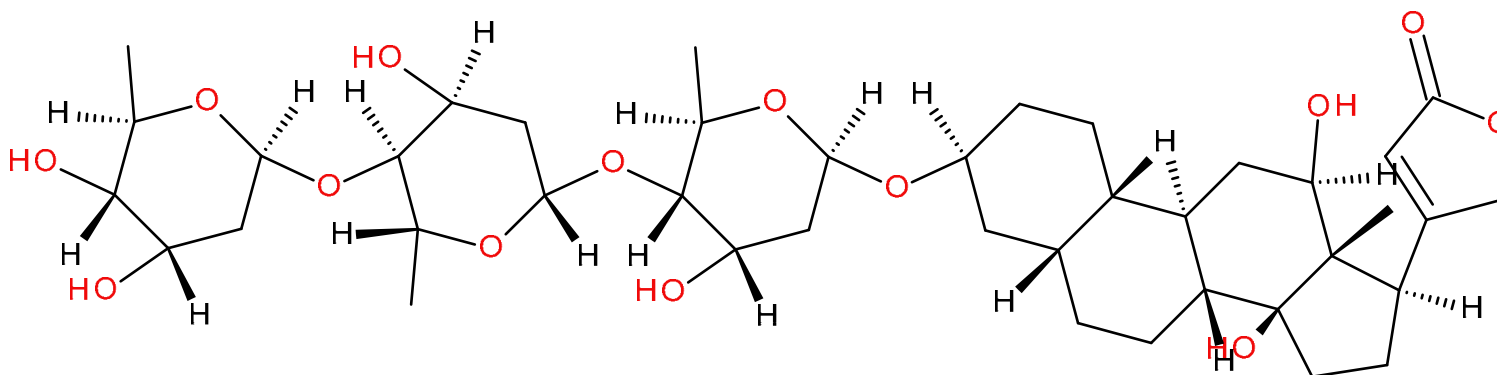
Regulation of inorganic solute transport



Cardiac P-type ATPases



- Na^+/K^+ -ATPase (ATP1A/ATP1B)
 - Heart failure, atrial fibrillation
 - [Digoxin](#) FDA pre-1975





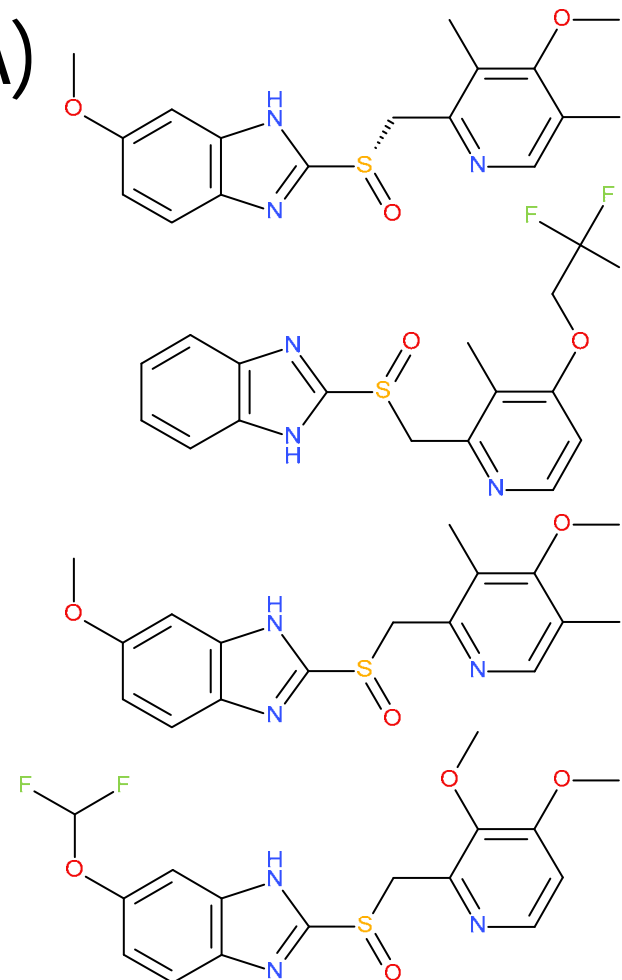
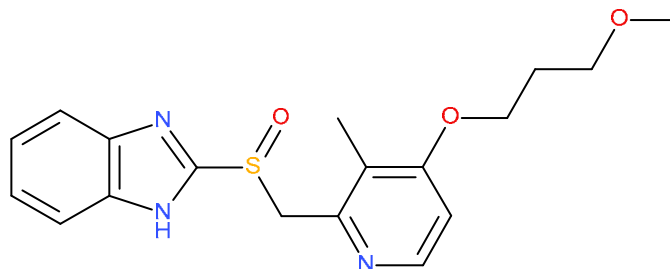
Gastric P-type ATPases



- H^+/K^+ -ATPase (ATP4A/ATP12A)

- Stomach/duodenal ulcer

- [Esomeprazole](#) FDA 2001
- [Lansoprazole](#) FDA 1995
- [Omeprazole](#) FDA 1989
- [Pantoprazole](#) FDA 2000
- [Rabeprazole](#) sodium FDA 1999

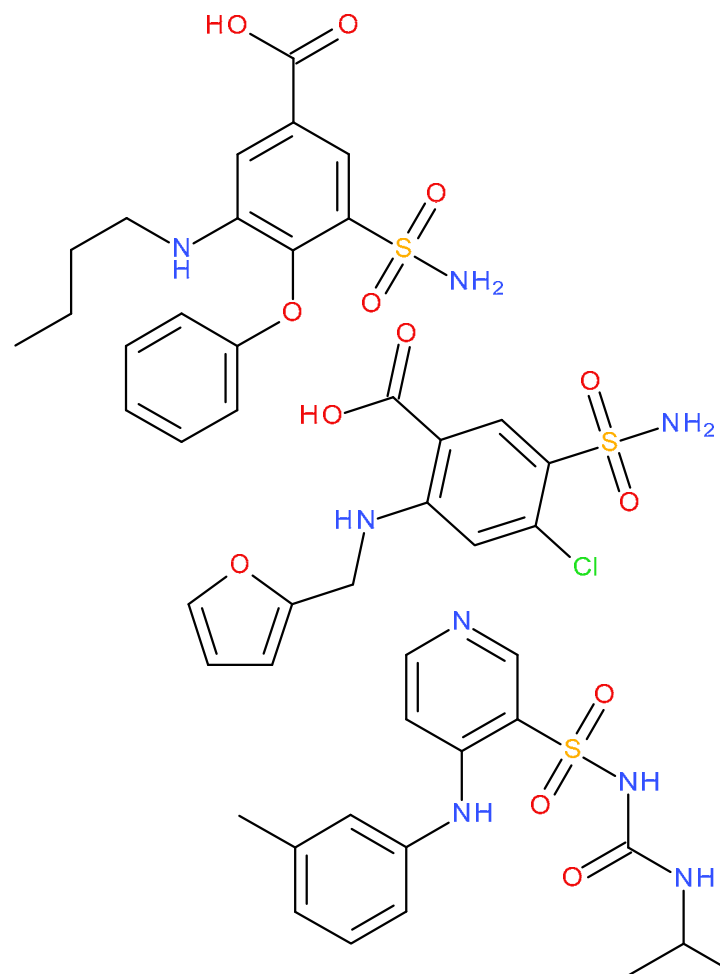




Renal SLC transporters



- NKCC2/SLC12A1
 - Oedema/hypertension
 - Bumetanide FDA 1983
 - Furosemide FDA 1966
 - Torasemide FDA 1993





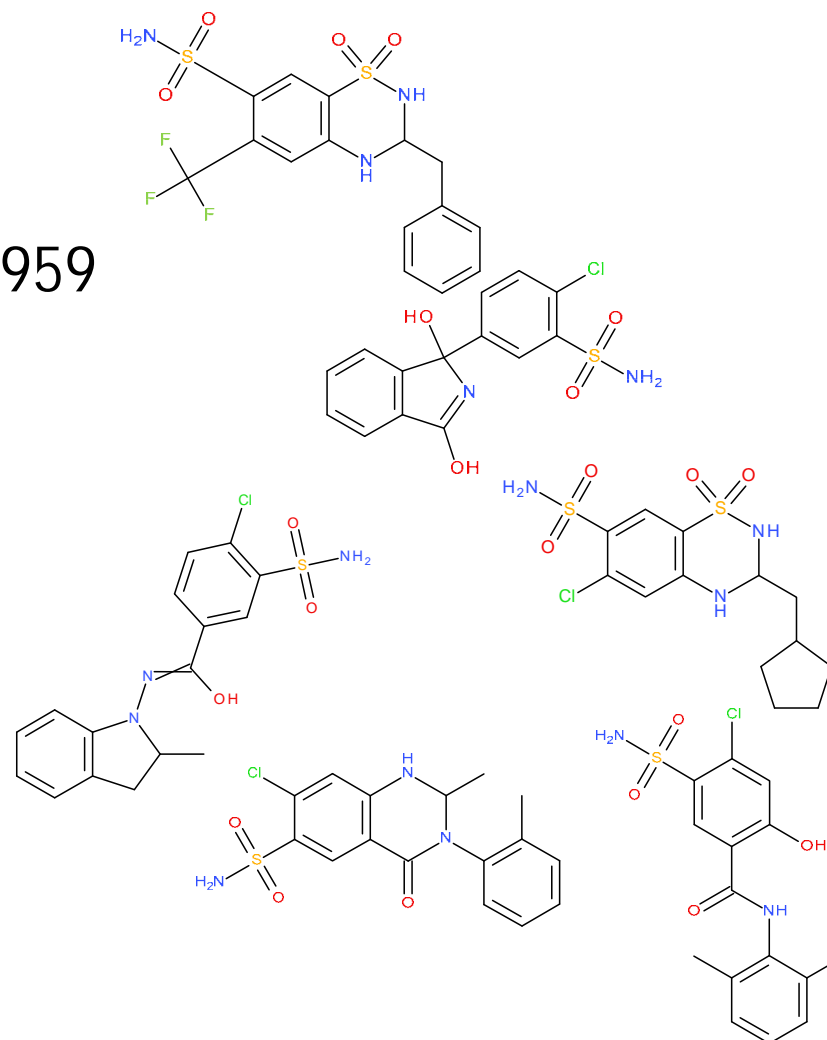
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Renal SLC transporters



- NCC/SLC12A3
 - Hypertension
 - Bendroflumethiazide FDA 1959
 - Chlortalidone FDA 1960
 - Carbonic anhydrase
 - Cyclopenthiazide
 - Indapamide FDA 1983
 - Metolazone FDA 1973
 - Xipamide EMA



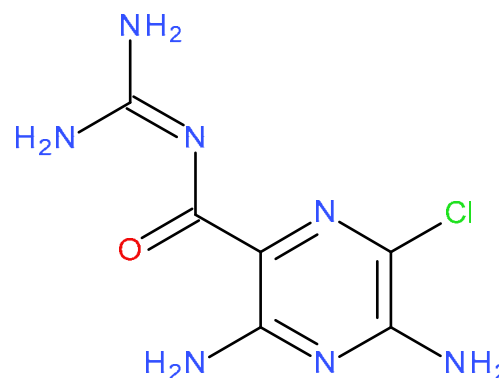
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Renal SLC transporters



- NHE1/SLC9A1
 - Oedoma
 - Amiloride FDA 1981
 - ENaC, ASIC, TRP ion channels





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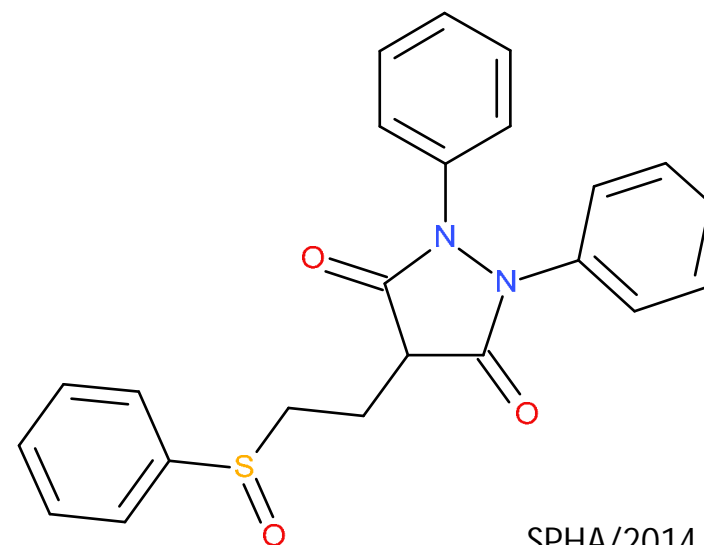
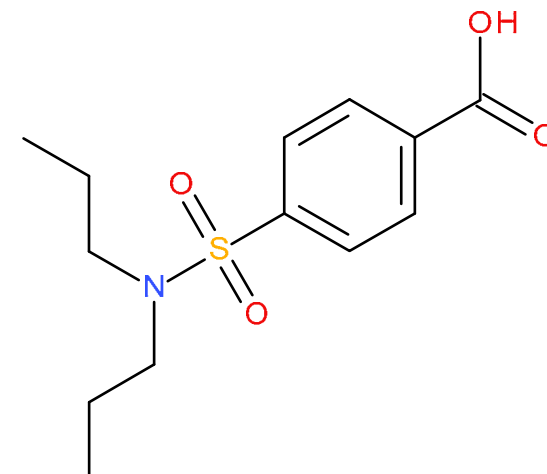
Regulation of organic solute transport



Renal SLC transporters



- URAT1/SLC22A12
 - Gout
 - Probenecid FDA 1951
 - OAT1/SLC22A6, NPT1/SLC17A1,
OATP1C1, TRPV2
 - Sulfinpyrazone FDA 1959
 - NPT1/SLC17A1

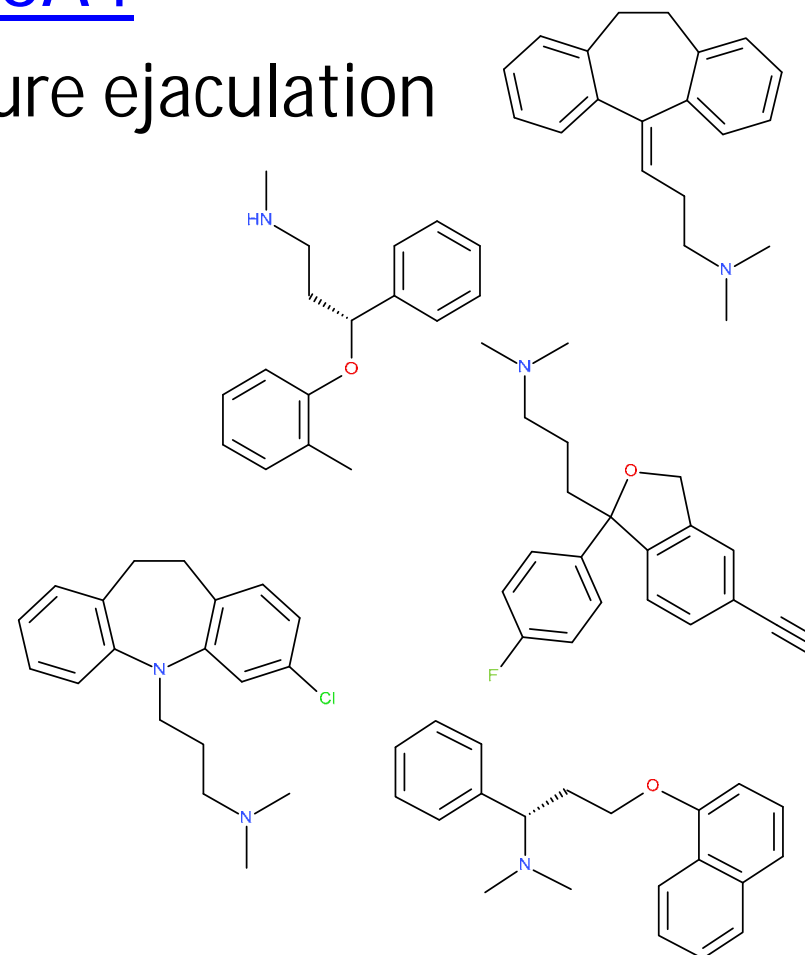




Neural SLC transporters



- NET/SLC6A2 and SERT/SLC6A4
 - Depression, ADHD, premature ejaculation
 - Amitriptyline HCl FDA 1961
 - Atomoxetine FDA 2002
 - Citalopram FDA 1998
 - Clomipramine HCl FDA 1989
 - Dapoxetine FDA 2004





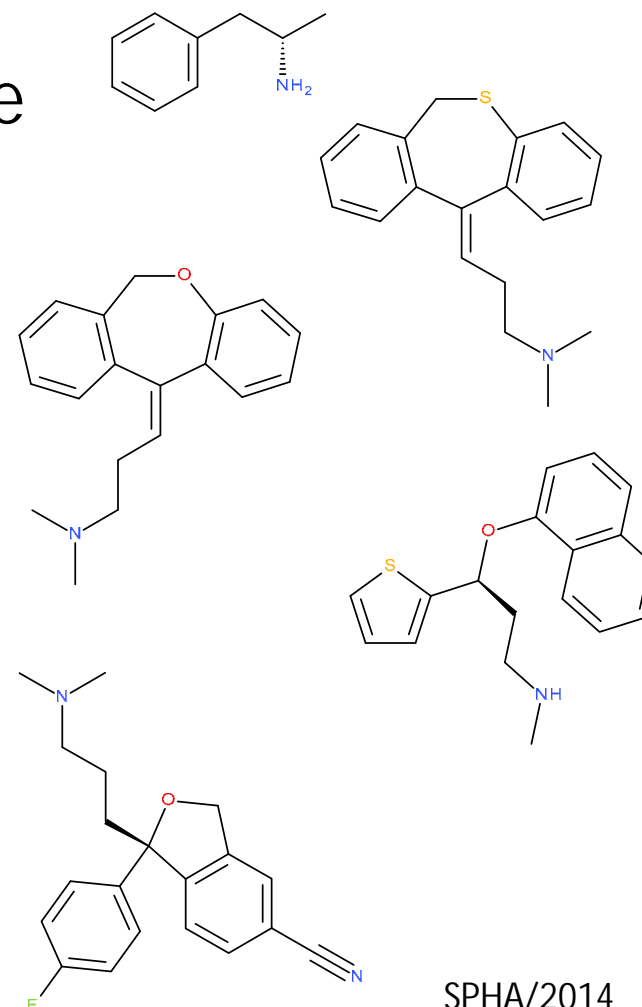
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Neural SLC transporters



- NET/SLC6A2 and SERT/SLC6A4
 - Depression, urinary incontinence
 - Dexamfetamine sulfate FDA 1975
 - Dosulepin HCl EMA
 - Doxepin FDA 1969
 - Duloxetine FDA 2004
 - Escitalopram FDA 2002



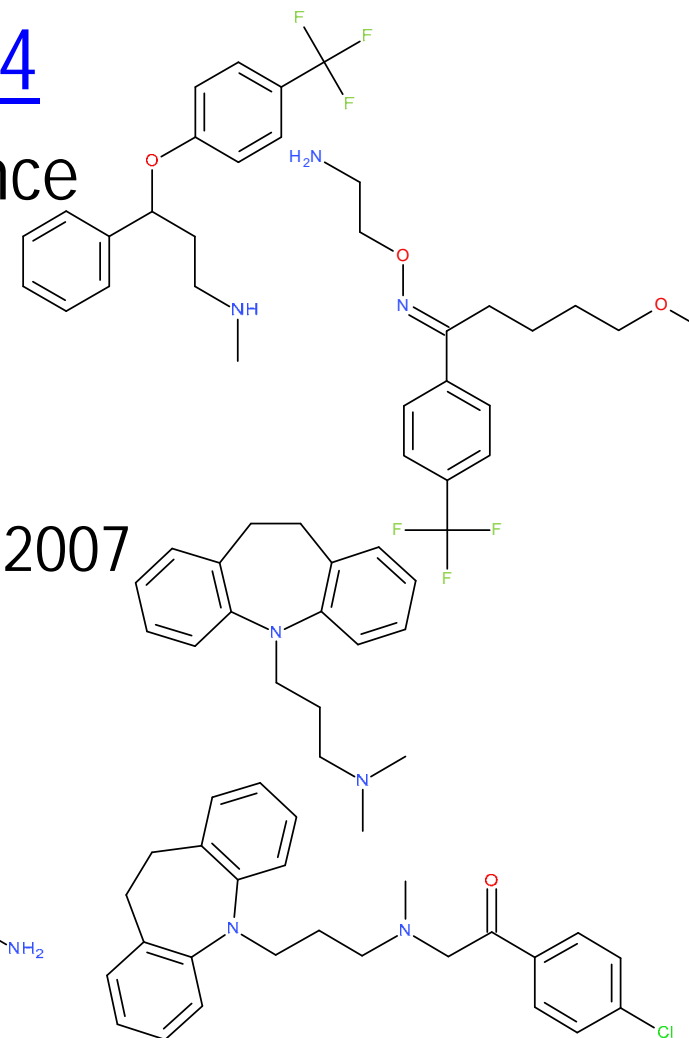
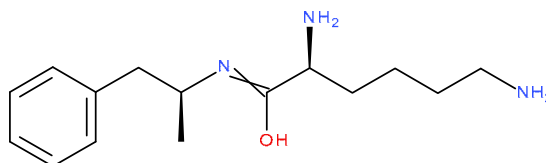
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Neural SLC transporters



- NET/SLC6A2 and SERT/SLC6A4
 - Depression, urinary incontinence
 - Fluoxetine FDA 1987
 - Fluvoxamine maleate FDA 1994
 - Imipramine HCl FDA 1959
 - Lisdexamfetamine mesilate FDA 2007
 - Lofepramine FDA 1983





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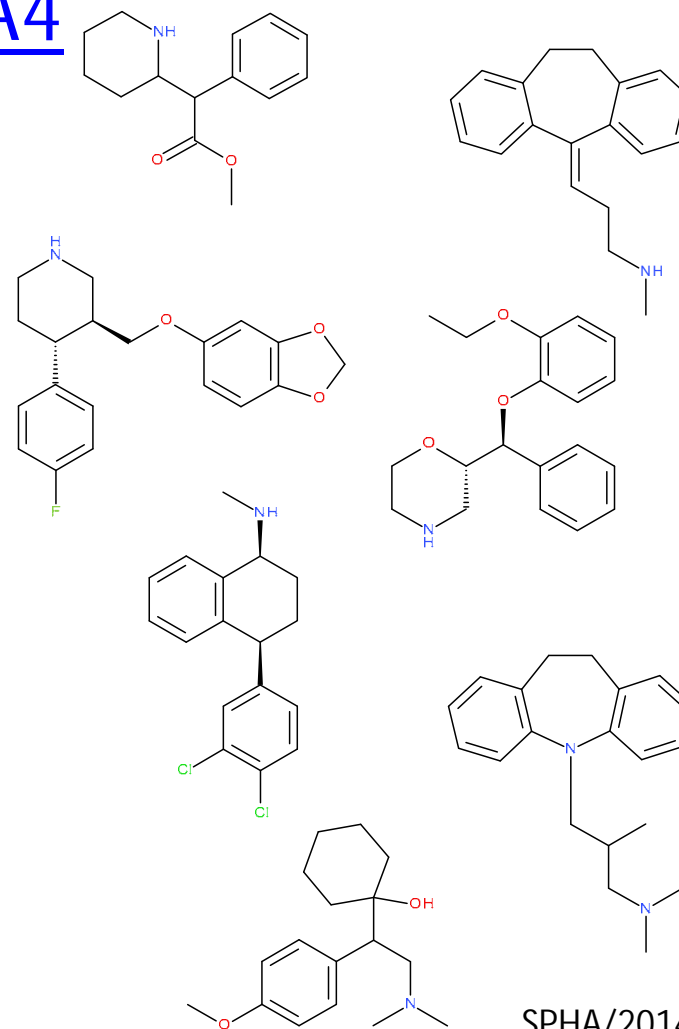
Neural SLC transporters



- NET/SLC6A2 and SERT/SLC6A4

- Depression, ADHD

- Methylphenidate HCl FDA 1955
- Nortriptyline FDA 1964
- Paroxetine FDA 1992
- Reboxetine
- Sertraline FDA 1991
- Trimipramine FDA 1979
- Venlafaxine FDA 1993



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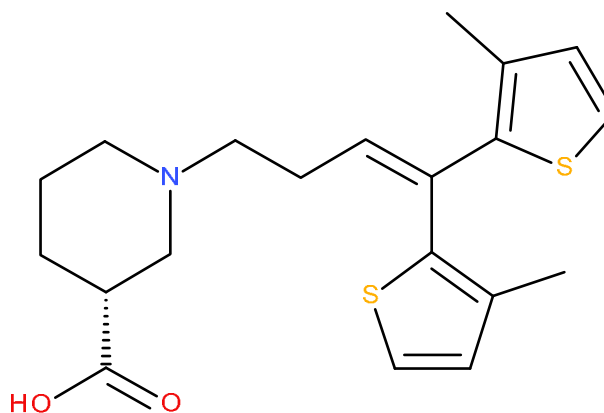
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Neural SLC transporters



- GAT1/SLC6A1
 - Anticonvulsant
 - Tiagabine FDA 1997





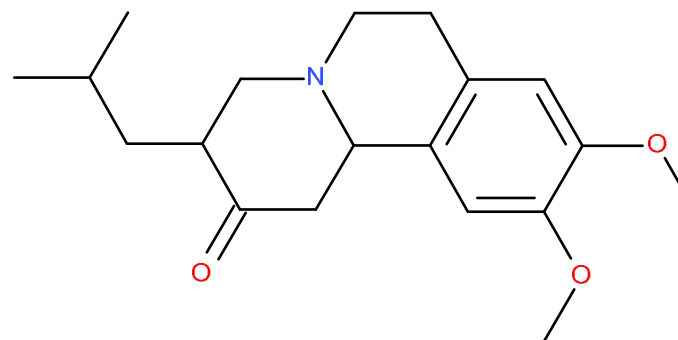
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Neural SLC transporters



- VMAT2/SLC18A2
 - Huntingdon's disease
 - Tetrabenazine FDA 2008





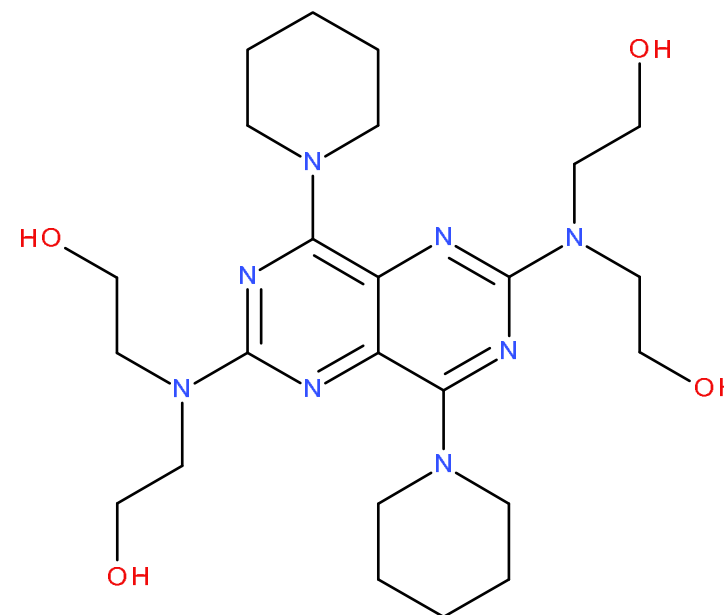
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Cardiovascular SLC transporters



- ENT1/SLC29A1
 - Thromboembolism
 - Dipyridamole FDA 1961
 - PDE7B, PDE8A

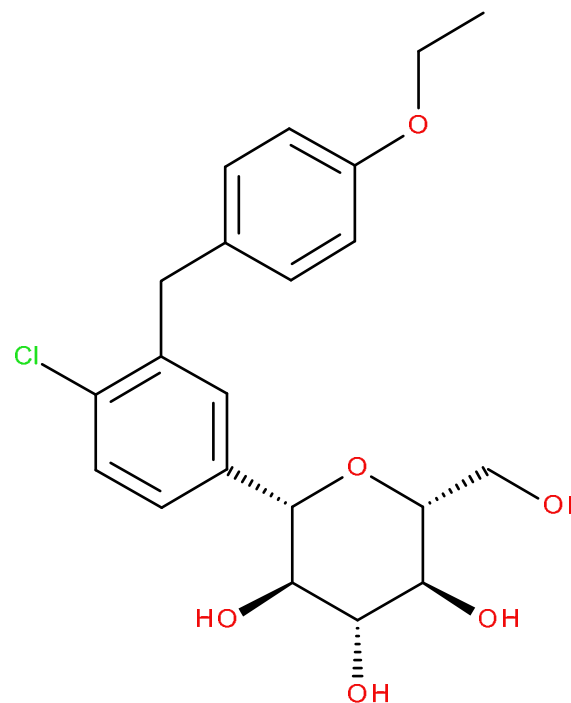




Renal SLC transporters



- SGLT2/SLC5A2
 - Type 2 diabetes
 - Dapagliflozin EMA 2012, FDA 2014

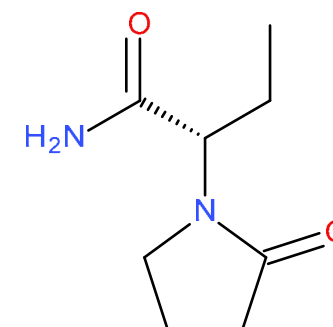
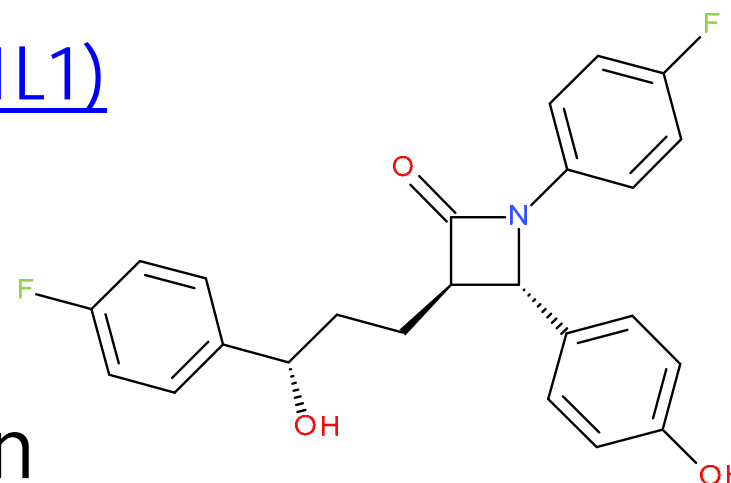




Other “transporters”



- Patched-like family
 - [Niemann-Pick C1-like 1 \(NPC1L1\)](#)
cholesterol transporter
 - Hypercholesterolaemia
 - [Ezetimibe](#) FDA 2002
- Synaptic vesicle glycoprotein
 - [SV2A](#)
 - Anticonvulsant
 - [Levetiracetam](#) FDA 1999

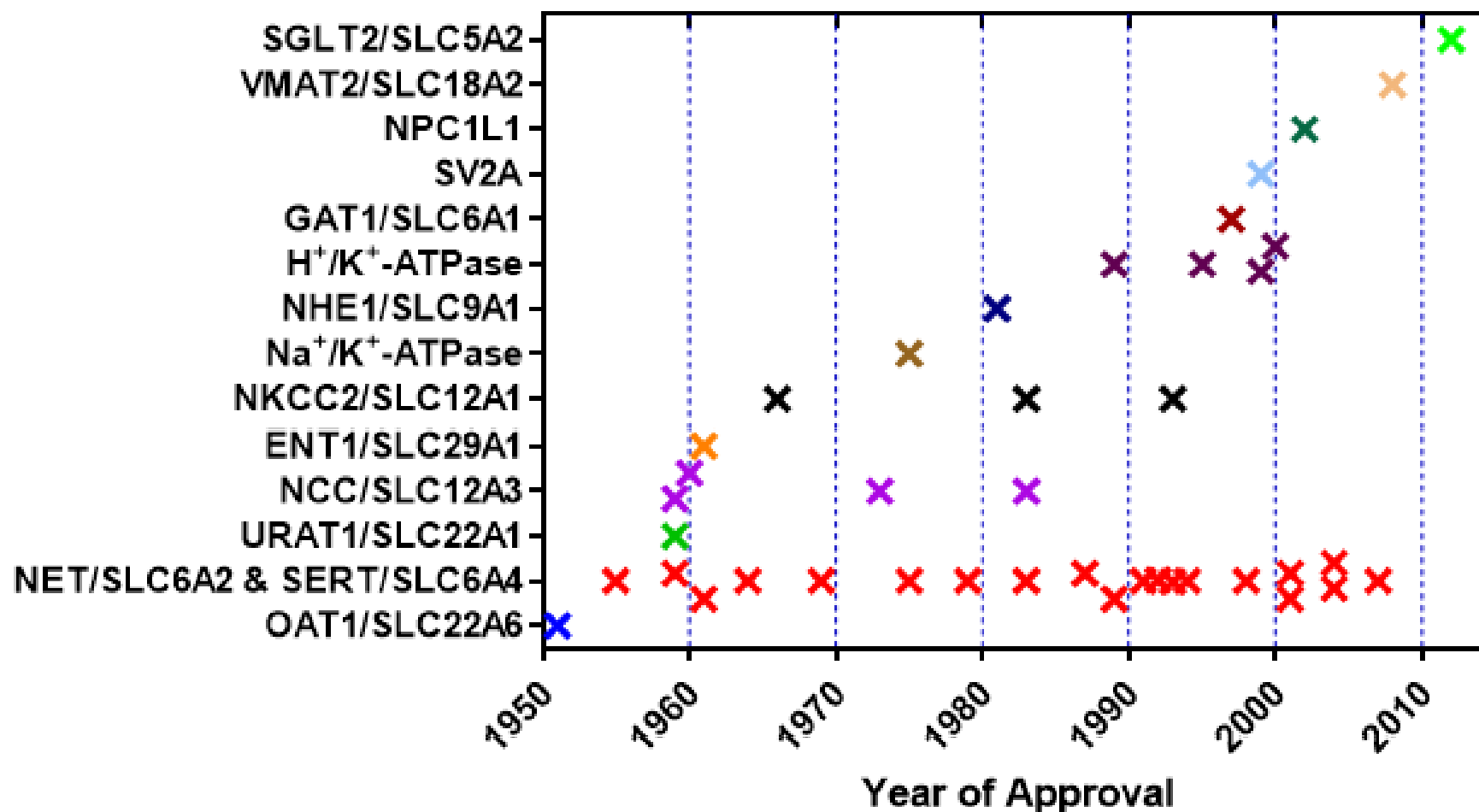




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Transporter-targetting drug approvals





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Transporters which are not TOADS

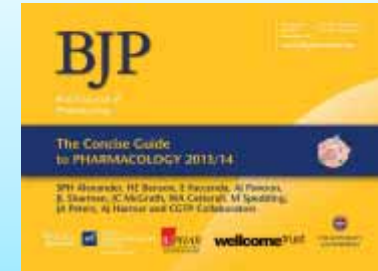
400+ genes



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For other medicinal drugs



- Transporters have a fundamental influence on ADME
 - Transporters in the GI tract influence bioavailability of drugs
 - Absorption
 - Transporters at the BBB determine CNS penetration of drugs
 - Distribution
 - Transporters in the liver influence hepatic uptake
 - Metabolism
 - Transporters in the kidney and liver influence renal and biliary export
 - Excretion



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TransPortal



- Kathy Giacomini (UCSF), supported by FDA
- Focussed on 32 transporters associated with drug disposition
 - ABCB1 (MDR1, P-gp); ABCB4 (MDR3); ABCB11 (BSEP); ABCC1 (MRP1); ABCC2 (MRP2, cMOAT); ABCC3 (MRP3); ABCC4 (MRP4); ABCC5 (MRP5); ABCC6 (MRP6); ABCG2 (BCRP, MXR)
 - OSTalpha (OSTA); OSTbeta (OSTB); SLC10A1 (NTCP); SLC10A2 (ASBT, SBAT2); SLC15A1 (PEPT1); SLC15A2 (PEPT2); SLC22A1 (OCT1); SLC22A2 (OCT2); SLC22A3 (OCT3); SLC22A4 (OCTN1); SLC22A5 (OCTN2); SLC22A6 (OAT1); SLC22A7 (OAT2); SLC22A8 (OAT3); SLC22A11 (OAT4); SLC22A12 (URAT1); SLC47A1 (MATE1); SLC47A2 (MATE2K); SLCO1A2 (OATP1A2, OATP-A); SLCO1B1 (OATP1B1, OATP-C, OATP2, LST-1); SLCO1B3 (OATP1B3, OATP8); SLCO2B1 (OATP2B1, OATP-B)
- ~480 ligands (substrates/inhibitors)



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Untransported drugs



- [Acarbose](#) (FDA 2007)
 - BBE disaccharidase inhibitor
 - Type 2 diabetes
- [Orlistat](#) (FDA 1999)
 - Pancreatic lipase inhibitor
 - Obesity



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RSC Drug Transporters Symposium: Target or Avoid?

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Summary



- Transporters: snog, marry or avoid?
 - 1194 agents in clinical usage in the UK
 - 2 (at least) avoid
 - 46 marry
 - All the others must snog, surely!