Geminal Heterodiatomic Motifs In Drug Design

Applications of Acetals, Ketals & their Sulfur & Nitrogen Analogues

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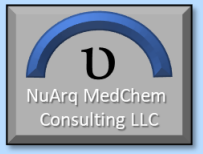
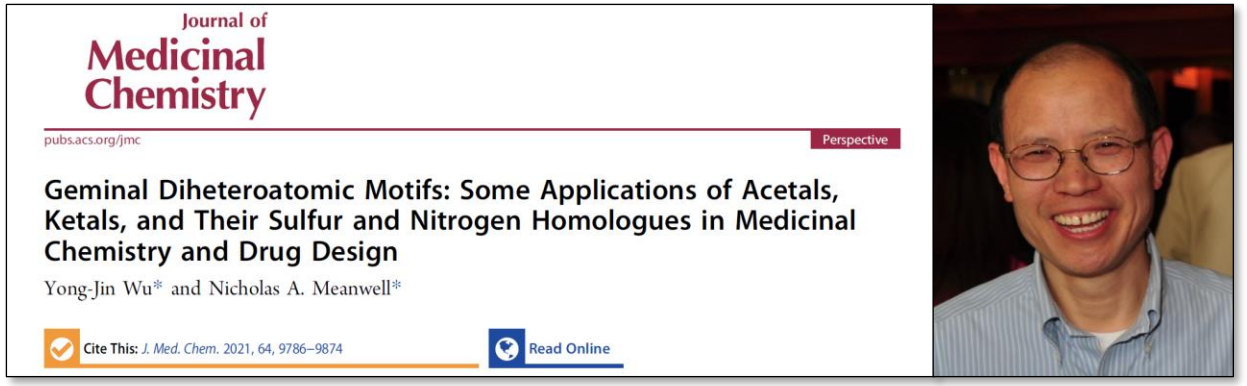


Baruch S. Blumberg Institute

Tuesday, October 3rd, 2023

Outline

- Preamble
  - prejudice/bias against geminal diheteroatomic motifs
- Background
  - geminal diheteroatomic motifs in Nature
  - marketed drugs with geminal diheteroatomic motifs
- Acetals and ketals in drug design
  - stabilizing acetals & ketals
  - a survey of applications of acetals & ketals
- *N,O*-Aminal and *N,N*-aminal derivatives
  - presence in marketed drugs & advanced compounds
  - examples from the antiviral literature
- Sulfur-containing geminal diheteroatomics
  - *O,S*-acetals
  - *N,S*-acetals
  - thioketals
- O-C-P derivatives
  - acyclic nucleoside phosphonates
  - α-hydroxy phosphonates
- Conclusion
- Acknowledgement



Preamble

- Geminal diheteroatomic motifs perceived as being potentially problematic
  - "*atypical*", "*unorthodox*"
  - potential for instability & degradation at the low pH of the GI tract
- But ….. there are many marketed drugs incorporate geminal diheteroatomic motifs
  - >90 examples built on both cyclic & acyclic topologies
    - O-C-O, O-C-N, O-C-S, N-C-N, N-C-S, S-C-S motifs are represented
  - compounds can exhibit good oral bioavailability, PK properties
- Chemical stability can readily be modulated by proximal functionality
  - design based on fundamental principles associated with the mechanism of hydrolysis
    - typically a proximal electron withdrawing substituent
  - provides an approach to enhance chemical stability for oral delivery
- Can be designed to degrade under acidic conditions
  - useful in prodrug design where immolation is required (no to be discussed)
- Geminal diheteroatomic motifs offer unique properties that can be exploited to advantage
  - modulate lipophilicity, H-bonding, conformation, biochemical reactivity
  - synthetic accessibility can be facile

Perceived Biases

"*1,3-dioxanes are not commonly found in active pharmaceutical agents due to their perceived instability*"

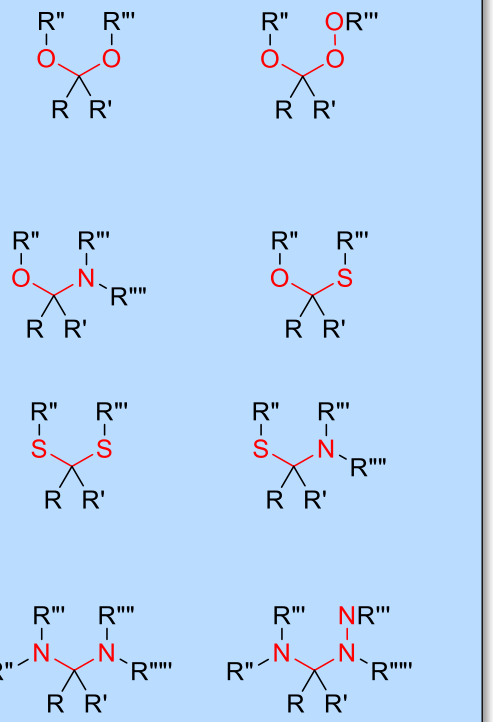
C.O. Ndubaku *et al., ACS Med. Chem. Lett*. 2015, **6**, 1241-1246

"*While 2-alkoxymorpholines are unusual cores in drug discovery, they are stable compounds that have produced marketed drugs*"

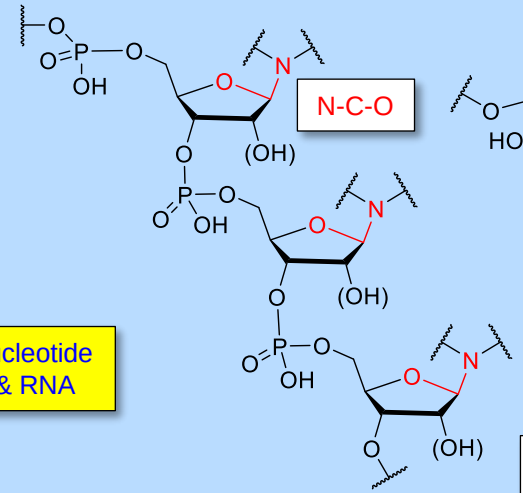
A.B. Bueno *et al., J. Med. Chem*. 2017, **60**, 9807-9820

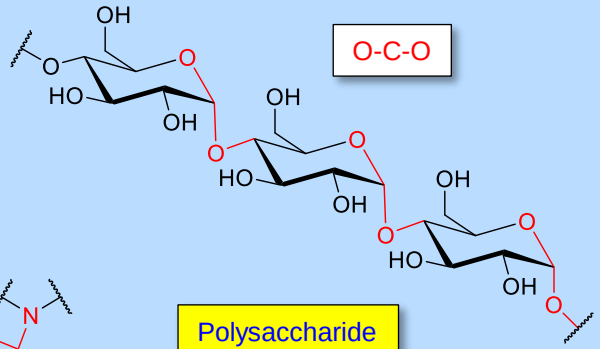
Natural Presence of Geminal Diheteroatomic Motifs

Geminal diheteroatomic motifs that have been explored in drug design



High prevalence in natural polymers

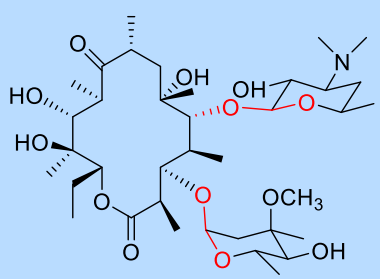


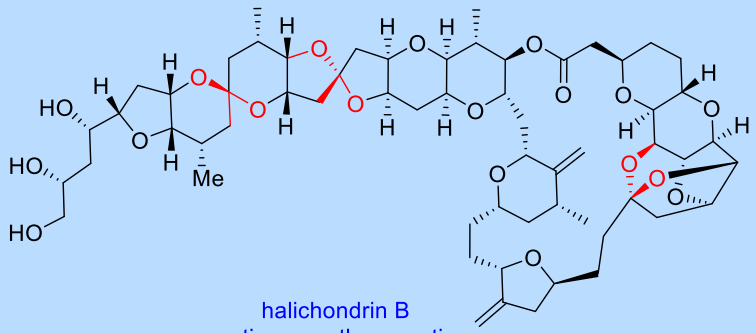


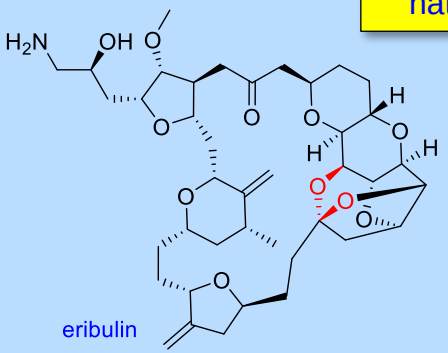
$t_{1/2}$ for N-C-O in DNA: 70-230 years at 25 °C
$t_{1/2}$ for O-C-O in saccharides: 10-1.2 x 10^7 years at 25 °C

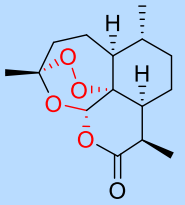
- 2 of the 3 natural polymers are built on geminal diheteroatomic motifs
  - assembly & disassembly mediated by enzymes

High prevalence in natural products


erythromycin A
antibiotic

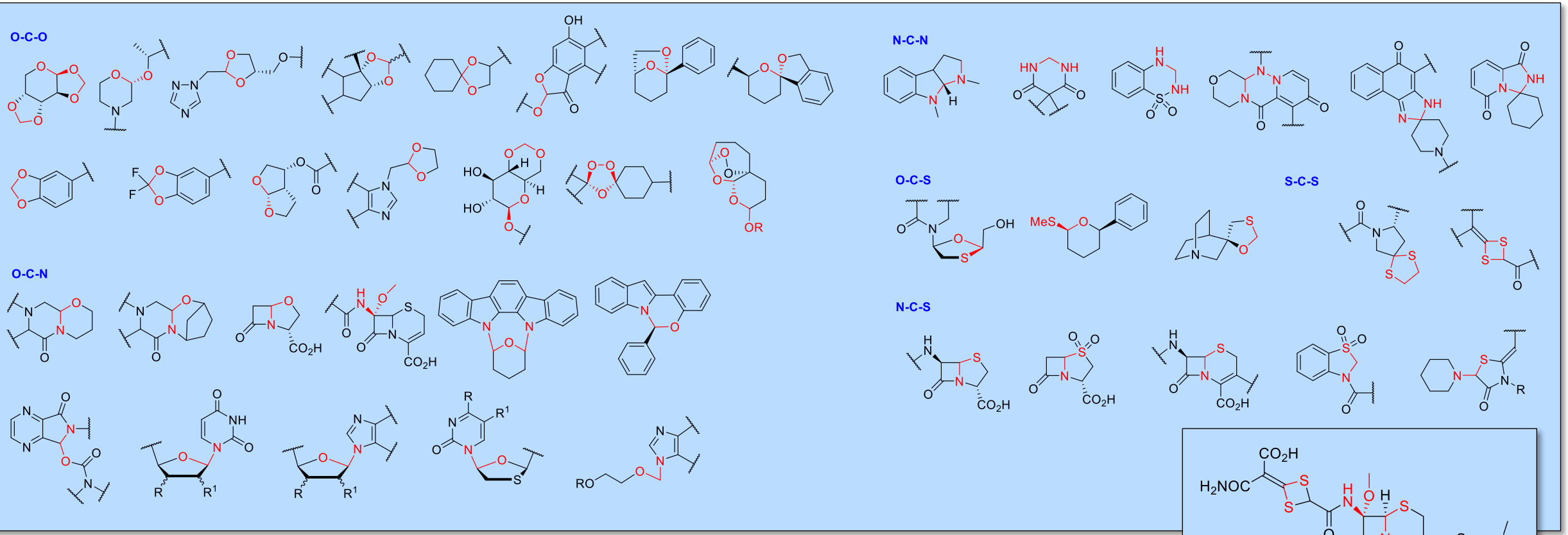

halichondrin B
anti-cancer therapeutic


eribulin


artemisinin
antimalarial

Y.-J. Wu & N.A. Meanwell, *J. Med. Chem.*, 2021, **64**, 9786-9874

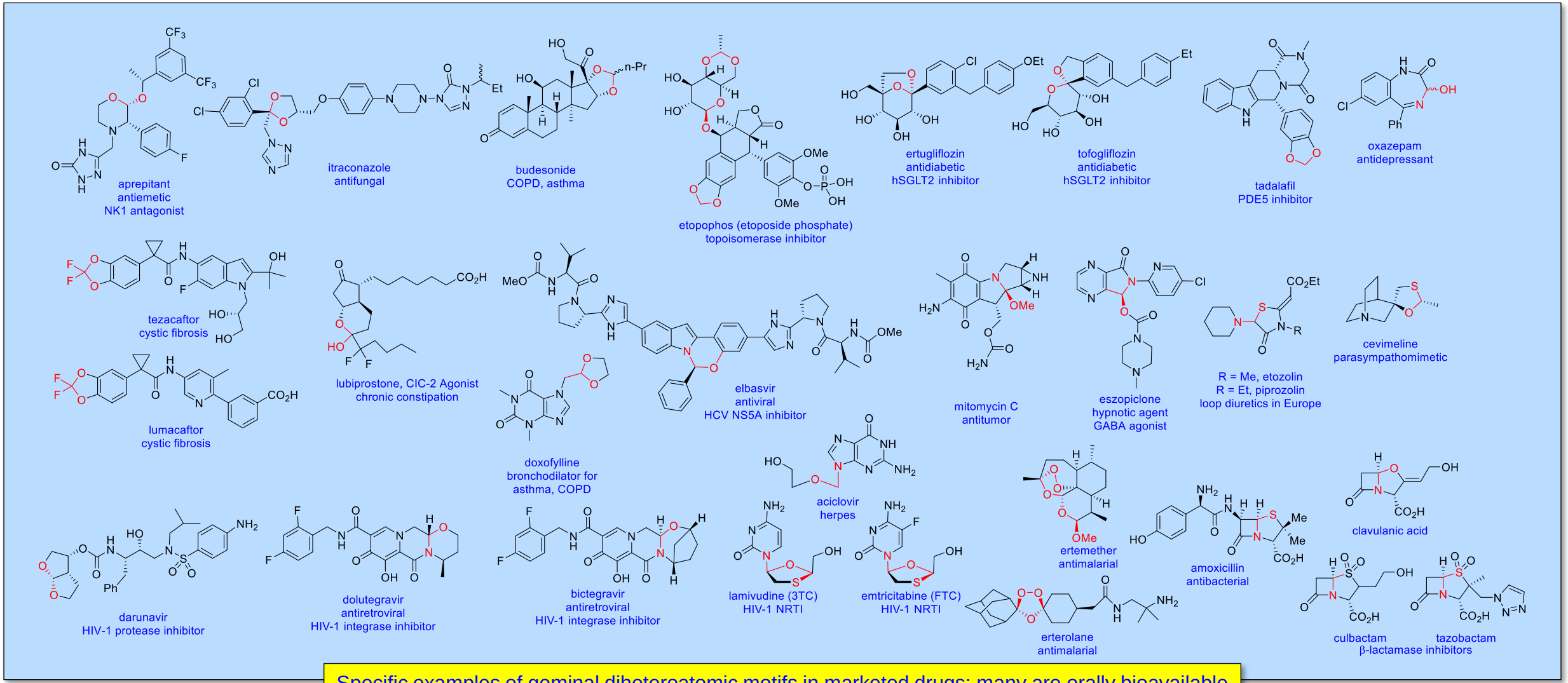
Geminal Diheteroatomic Motifs in Marketed Drugs



- Geminal diheteroatom motifs are well-represented in marketed drugs
  - prevalent in preclinical compounds
- Wide range of motifs have been explored
  - ketals, acetals, aminals & hemiaminals, thioaminals, thioketals & thioacetals
- β-Lactam antibiotics present a particularly interesting series of examples
  - strained ring systems that rely upon chemical reactivity for biological effects
  - cefotetan (injectable) is rich in geminal diheteroatomic motifs: S-C-S, N-C-O, N-C-S

Y.-J. Wu & N.A. Meanwell, *J. Med. Chem.*, 2021, **64**, 9786-9874

Geminal Diheteroatomic Motifs in Marketed Drugs



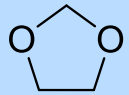
Specific examples of geminal diheteroatomic motifs in marketed drugs; many are orally bioavailable

Y.-J. Wu & N.A. Meanwell, *J. Med. Chem.*, 2021, **64**, 9786-9874

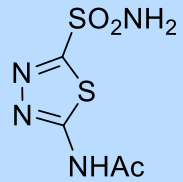
Acetals and Ketals in Drug Design

Topiramate: a Successful Anticonvulsant

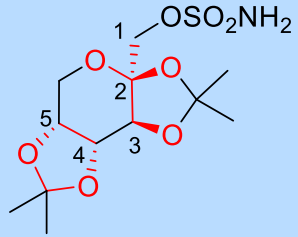
Incorporates 3 Embedded Ketal Elements – 2 are Derived from Acetone



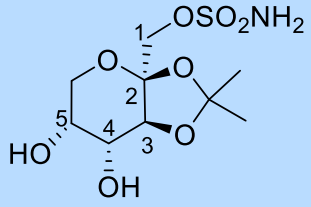
5th most prevalent oxygenated ring in marketed drugs
24 examples



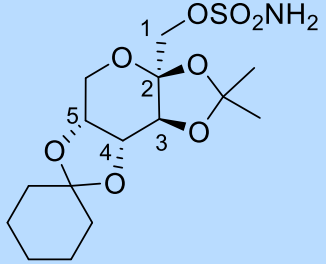
acetazolamide
anticonvusant



topiramate
anticonvulsant
F = 80%; $t_{1/2}$ = 21 h
CSF/Plasma = 0.85



inactive



inactive

Launched in 1996

68th most commonly prescribed drug in U.S. in 2019
- 10 million prescriptions

Peak annual sales of $2.2 bn

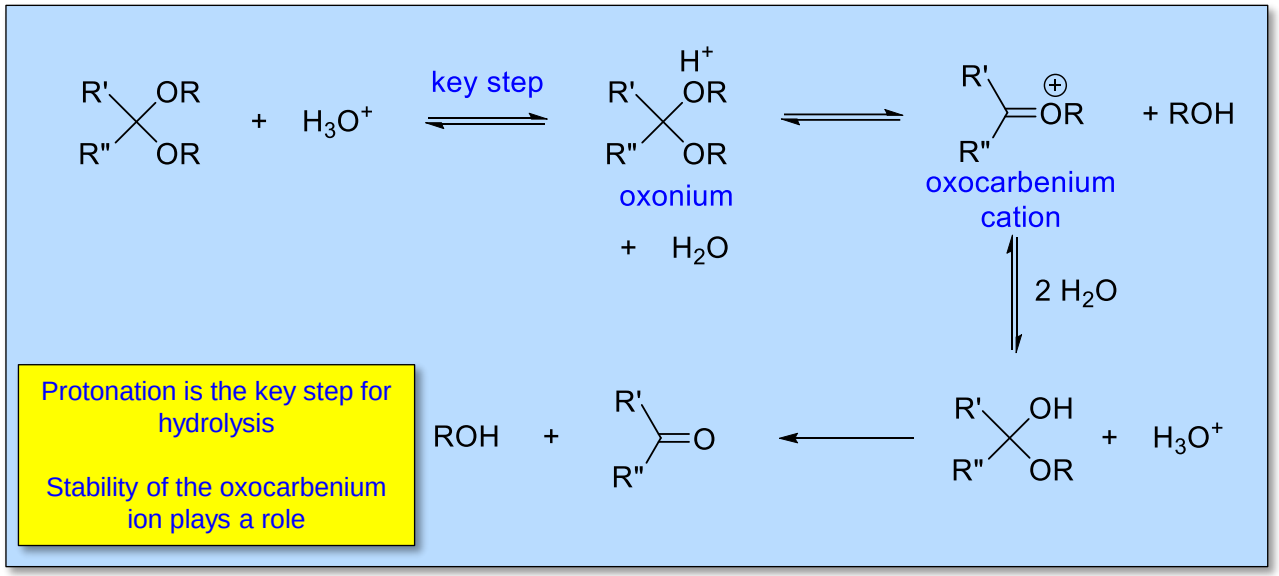
Bruce E. Maryanoff

"As the inventor of topiramate, which contains two ketal groups, I have to say how much flack I caught in trying to champion clinical development of the compound. Bunch of naysayers out there, with inherent chemical prejudices. We verified its stability to simulated gastric fluid and the rest is history: a billion-dollar drug!"

https://blogs.sciencemag.org/pipeline/archives/2015/11/05/another-funny-looking-structure-comes-through

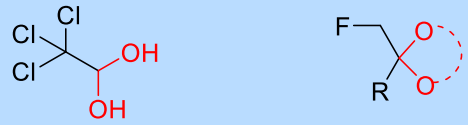
B.E. Maryanoff, *ACS Med. Chem. Lett.*, 2016, **7**, 662-665; B.E. Maryanoff *et al.*, *J. Med. Chem.*, 1998, **41**, 1315-1343; J.T. Njardarson *et al., J. Med. Chem.*, 2018, **61**, 10996-11020

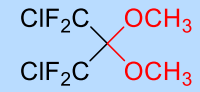
Ketal Hydrolysis: Mechanism & Implications for Modulation



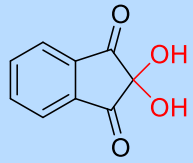
Protonation is the key step for hydrolysis

Stability of the oxocarbenium ion plays a role

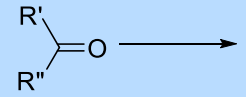




electron-deficient C=O derivatives
- stable hydrates
- enhanced stability toward hydrolysis



- Formation of resonance-stabilized oxonium ion is the rate-determining step
  - protonation of O followed by elimination of ROH
  - applies to the majority of dialkyl ketals
- Electron withdrawing groups decrease the rate of acid-mediated hydrolysis
  - reduce O basicity & the propensity for protonation
  - destabilize the oxonium ion intermediate
- Electron deficient C=O moieties readily hydrate to acetals or hemiacetals
  - extent of hydration depends on properties of the electron withdrawing moiety
- Concepts extend to hydrolysis of other geminal diheteroatomic motifs
  - N-C-O; N-C-S; S-C-O; S-C-S



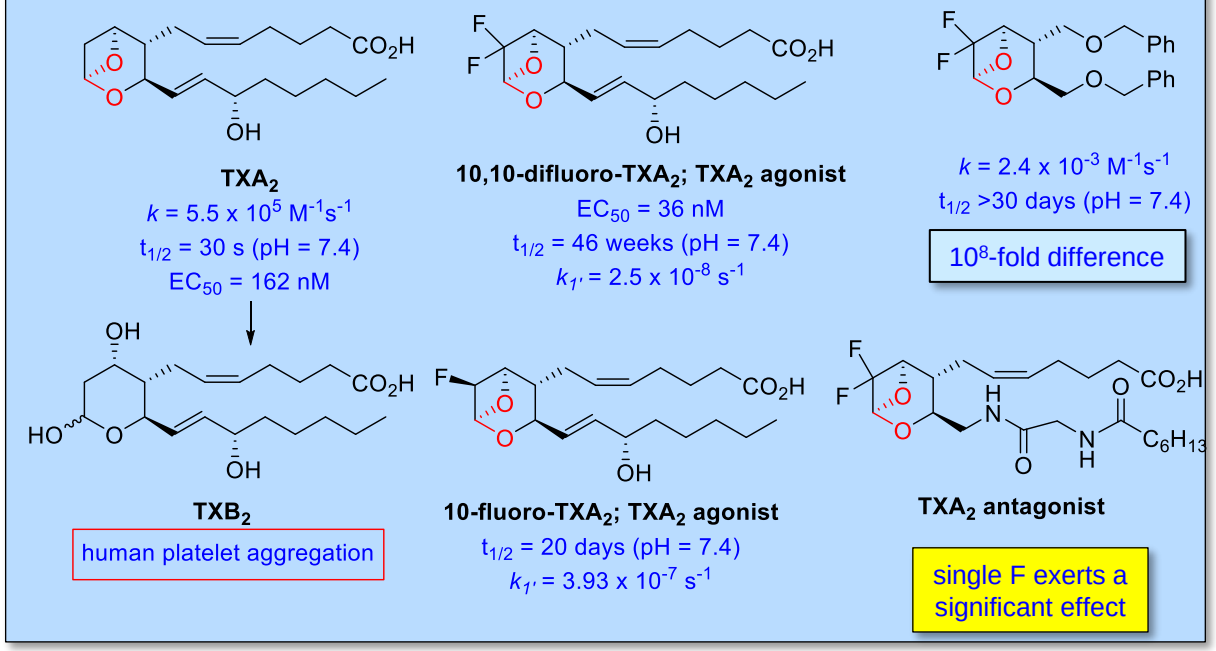
Carbonyl Compound	Hydration K_{eq}	Hemiacetal K_{eq}
CH_3CHO	1.06	0.50*
CF_3CHO	2.9×10^4	1.2×10^3
CH_3COCH_3	1.4×10^{-3}	2.2×10^{-4}
CF_3COCH_3	35	0.88
CF_3COCF_3	1.2×10^6	3.0×10^3

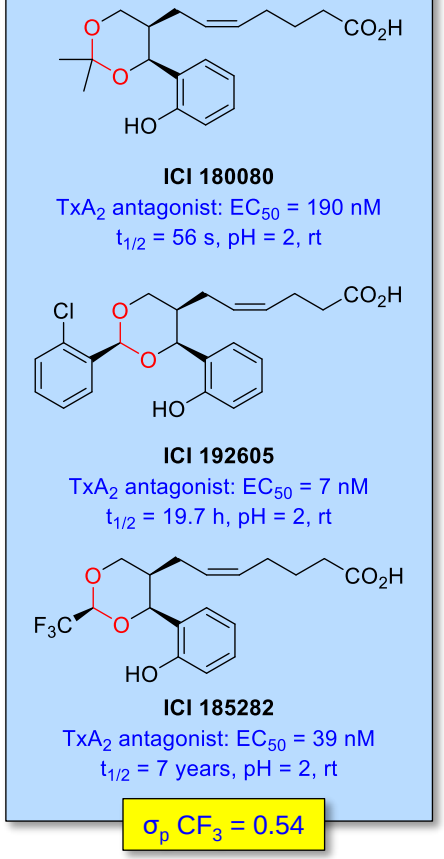
Hemiacetal *K* measured in MeOH except * (EtOH)

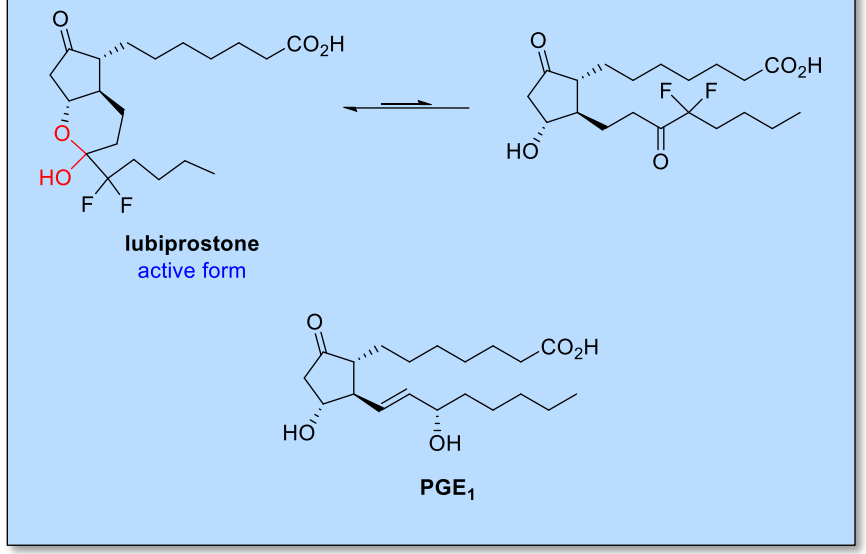
CF_3 confers 10^4 Δ

J.P. Guthrie, *Can. J. Chem.*, 1974, **53**, 898-906; H.E. Simmons & D.W. Wiley, *J. Am. Chem. Soc.*, 1960, **82**, 2288-2296
S.L. Schreiber *et al., Chem. Biol.*, 2000, **7**, 275-286; D. Ma *et al.*, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3849-3852

Hydrolytic Stability of Fluorinated Ketals, Acetals, Hemiketals







- TxA_2 is chemically unstable
  - highly reactive ketal due to ring strain
  - hydrolyzes spontaneously in aqueous media: $t_{½}$ = 30 sec
  - TXB_2 is inactive
- 10,10-difluoro substitution enhances stability
  - 10^8-fold lower rate of hydrolysis for model compound
- TxA_2 antagonist series based on 1,3-dioxane scaffold
  - acetal moiety stabilized by electron withdrawing substituents
- CF_3 substituent the most effective
  - $t_{1/2}$ = 7 years: ~4 x 10^6 more stable than the diMe ketal at pH = 2

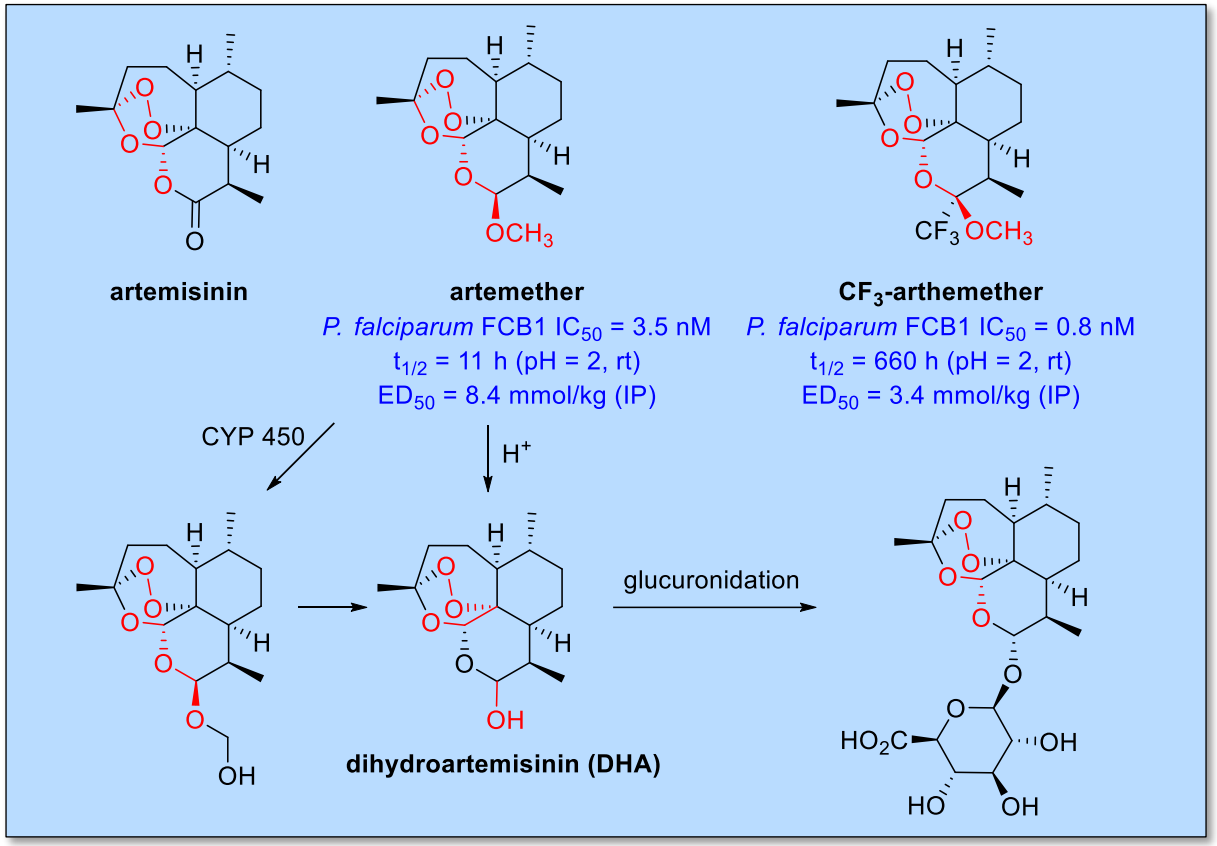
- CIC-2 chloride channel agonist
  - used to treat chronic constipation
  - minimal systemic exposure
- CF_2 enhances stability of the hemiketal
  - stabilizes the active form of the drug

E. Raschi & F. De Ponti,
Exp. Opin. Drug Metab. Toxicol., 2014, **10**, 293-305

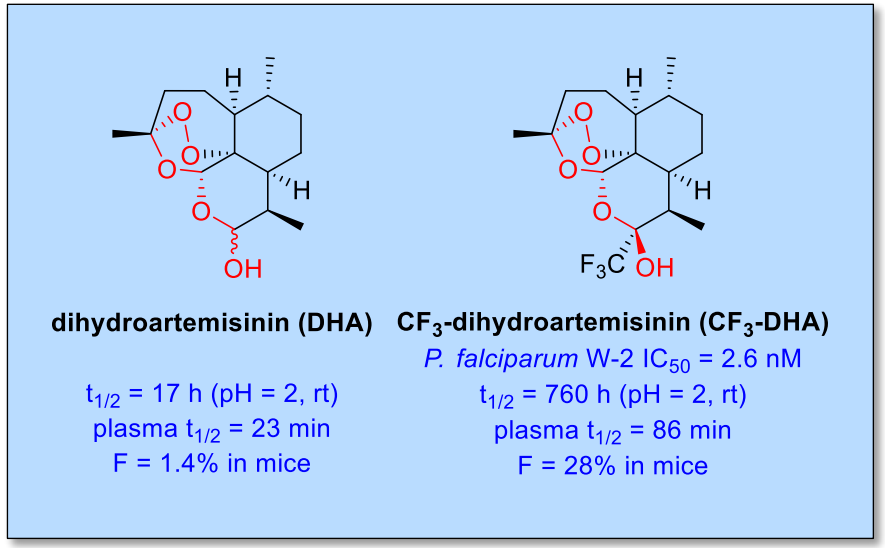
Prostanoids

J. Fried *et al*., *JACS* 1989, **111**, 4510-4511; *J. Org. Chem*. 1993, **58**, 5724-5731; *Proc. Natl. Acad. Sci. USA,* 1989, **86**, 5600-5604; E.J. Corey *et al*., *JACS*, 1981, **103**, 6502-6505
V.K. Aggarwal *et al., ACS Cent. Sci*. 2020, **6**, 995-1000; J.L. Longridge *et al*., *J. Chem. Soc. Perkin 2*, 1990, 965-970; A.G. Brewster *et al*., *Prostaglandins*, 1988, **36**, 173-178

Stabilizing a Labile Acetal: CF_3-Artemether & CF_3-Artemesinin



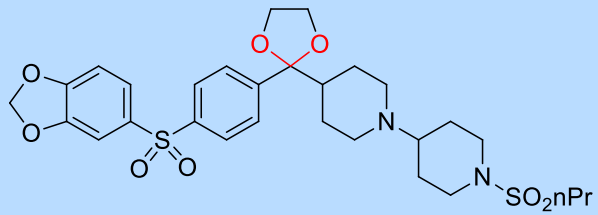
- Artemether possesses a short $t_{1/2}$ due to low chemical & metabolic stability
  - DHA is rapidly eliminated *via* phase 2 glucuronidation metabolism
- CF_3 substitution enhances acid stability by 60-fold
  - improves activity *in vivo* by 2-fold
  - reduced levels of glucuronide *in vivo*



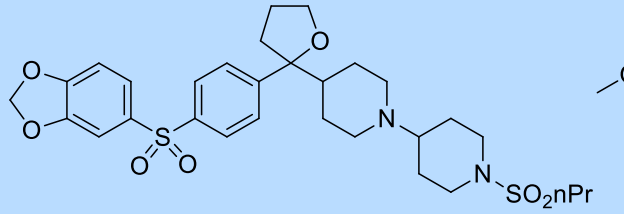
- CF_3 improved chemical acid stability by 45-fold
  - plasma stability enhanced by 4-fold
  - oral F increased by 20-fold
- CF_3-DHA showed better in vivo activity
  - longer plasma $t_{1/2}$
  - enhanced chemical stability
  - reduced phase 2 glucuronidation

J.-P. Begue *et al.*, *Fluorine in Med. Chem. Chem. Biol.*, 2009, 142-163; P.D. Binh *et al.*, *Trans. Royal Soc. Trop. Med. Hygiene*, 2002, **96**, 677-683
G. Magueur *et al.*, *J. Med. Chem.*, 2004, **47**, 2694-2699

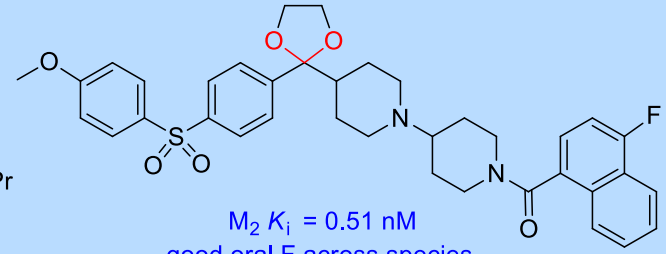
Stabilizing Ketals: Benzylidene Ketals in M_2 Muscarinic Antagonists



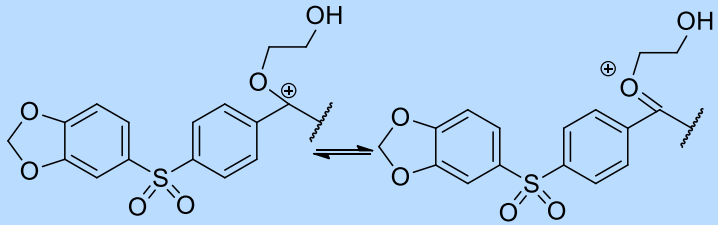
M_2 K_i = 0.01 nM
stable in 0.1 N HCl for several days
poor oral activity in monkeys



M_2 K_i = 5 nM
500x weaker



M_2 K_i = 0.51 nM
good oral F across species



destabilized by SO_2

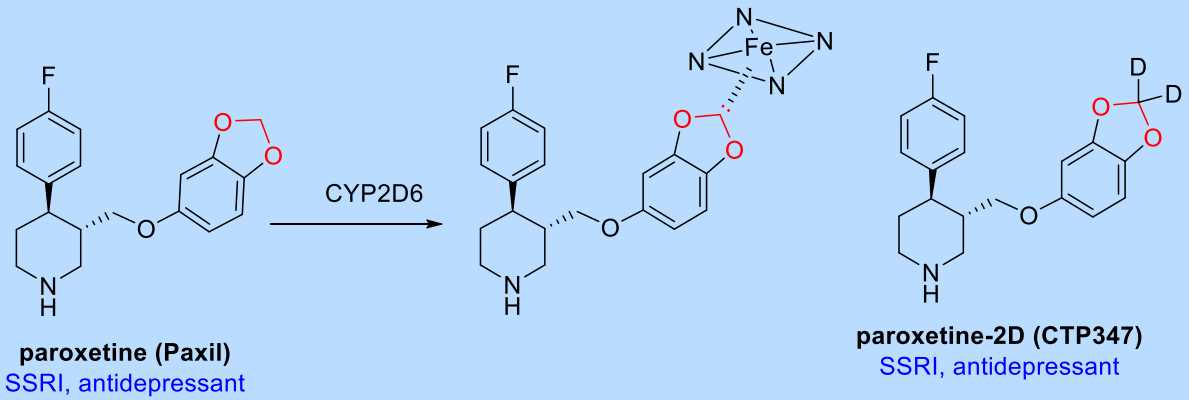
σ_p CH_3SO_2 = 0.72
σ_p CF_3SO_2 = 0.92
σ_p CF_3 = 0.54

- Potent & selective muscarinic M_2 antagonist
  - dioxolane ketal is chemically and metabolically stable
- Acid stability is presumably a function of the e-withdrawing SO_2Ar moiety
  - reduces propensity for protonation of O atoms
  - destabilizes oxonium/carbenium ion
- Basic piperidine *N* adds to the chemical stability
  - protonation of *N* discourages 2nd protonation

- Ketal is important for potency
  - O to CH_2 in ketal reduced M_2 potency by 500-fold
  - M_1 & M_3 potency maintained → reduced selectivity
- Rapid clearance of methylenedioxy compounds in cyno monkey
  - methylenedioxy moiety undergoes CYP-mediated cleavage
- Replaced with simple OMe
  - naphthalene ring fluorinated to enhance metabolic stability
  - compound shows good oral F across species

C.D. Boyle *et al*., *Bioorg. Med. Chem. Lett*., 2000, **10**, 2727-2730; 2001, **11**, 2311-2314

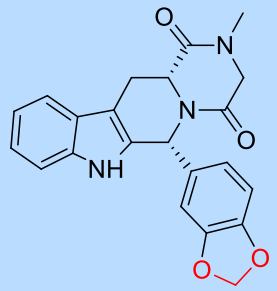
1,3-Benzodioxoles: Chemically Stable; Metabolically Problematic



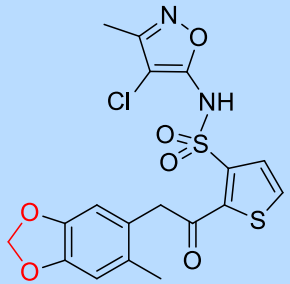
paroxetine (Paxil)
SSRI, antidepressant

paroxetine-2D (CTP347)
SSRI, antidepressant

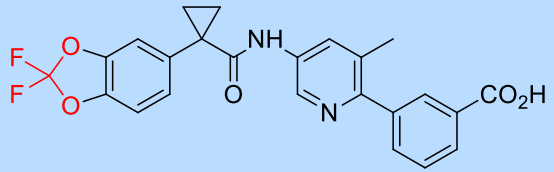
- Acid-stable element widely distributed in Nature
  - metabolic stability can be problematic
- Paroxetine irreversibly inactivates CYP2D6
  - inhibits its own metabolism
    - plasma levels ~10-fold higher after 2 weeks of dosing
  - precipitates DDIs with other medications metabolized by CYP2D6
- Methylenedioxy metabolized by CYP2D6 to give carbene
  - carbene binds tightly to the heme Fe & inhibits enzyme function
  - further metabolism can lead to *ortho*-quinone formation
- Deuteration slows carbene formation; lessens inactivation of the enzyme
  - di-F substitution blocks formation of the carbene intermediate



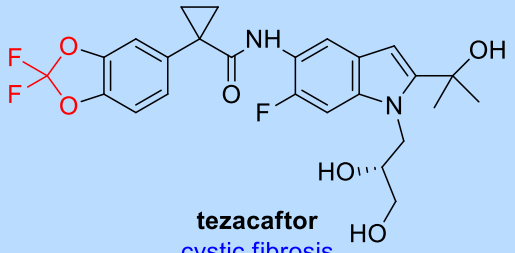
tadalafil
PDE5 inhibitor



sitaxsentan
endothelin antagonist
withdrawn 2010 due to liver toxicity



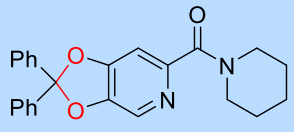
lumacaftor
cystic fibrosis



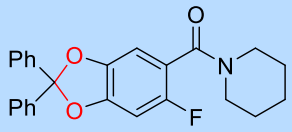
tezacaftor
cystic fibrosis

T. Pirali *et al*., *J. Med. Chem*., 2019, **62**, 5276-5297; E. Gillis *et al., J. Med. Chem*., 2015, **58**, 8315-8359; N.A. Meanwell, *J. Med. Chem*., 2018, **61**, 5822-5880

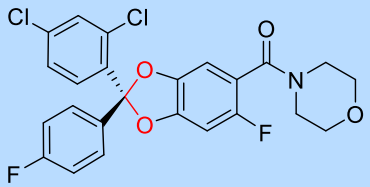
Stabilizing Diphenylated 1,3-Benzodioxoles



hCB1 *Ki* = 5 nM
unstable in weakly acidic media



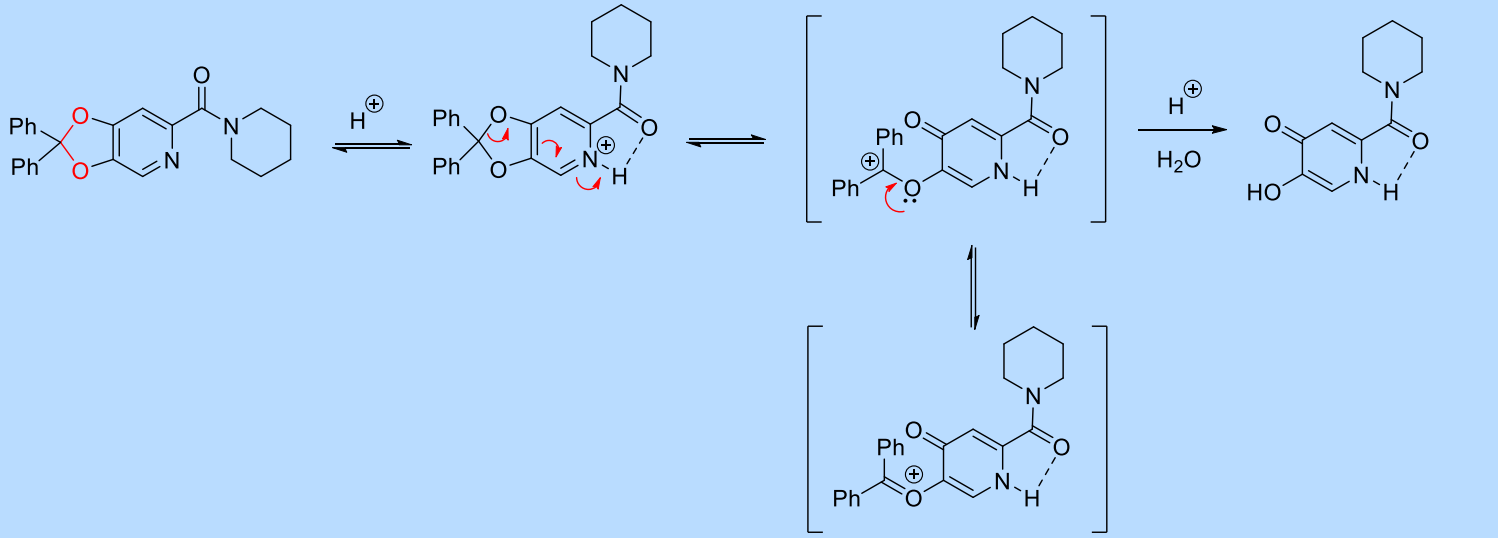
hCB1 *Ki* = 11 nM
more stable in weakly acidic media



good acid and metabolic stability
hCB1 *Ki* = 3.3 nM
hCB1 EC_{50} (cAMP)= 8 nM (inverse agonist)
hypothermia assay ID_{50} = 4 mpk
body weight reduction in DIO rat model: 4.6% @ 10 mpk (PO)

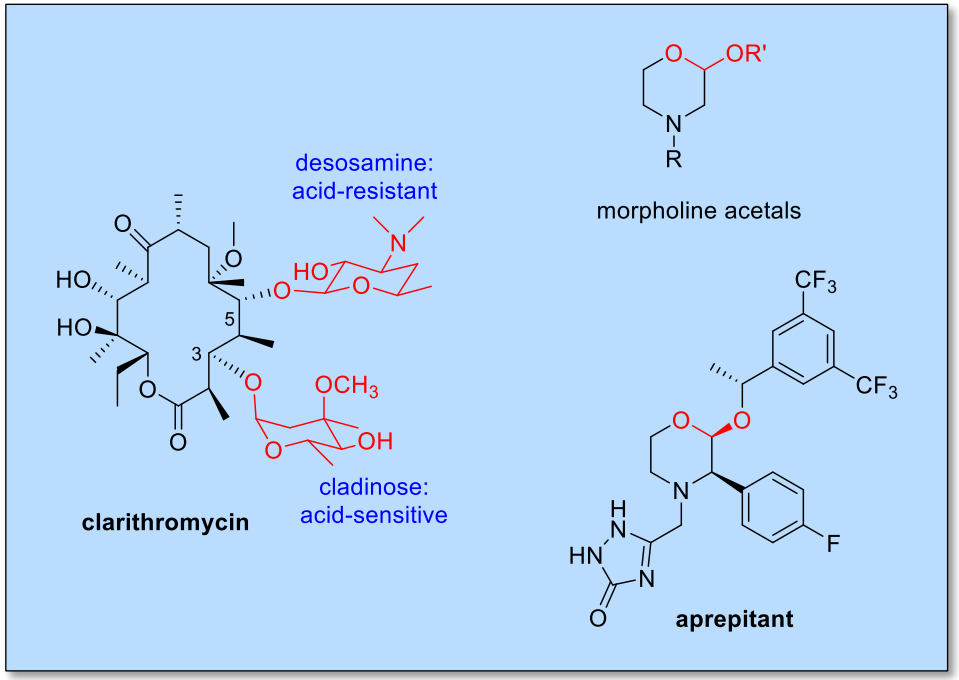
CB-1 inverse agonists

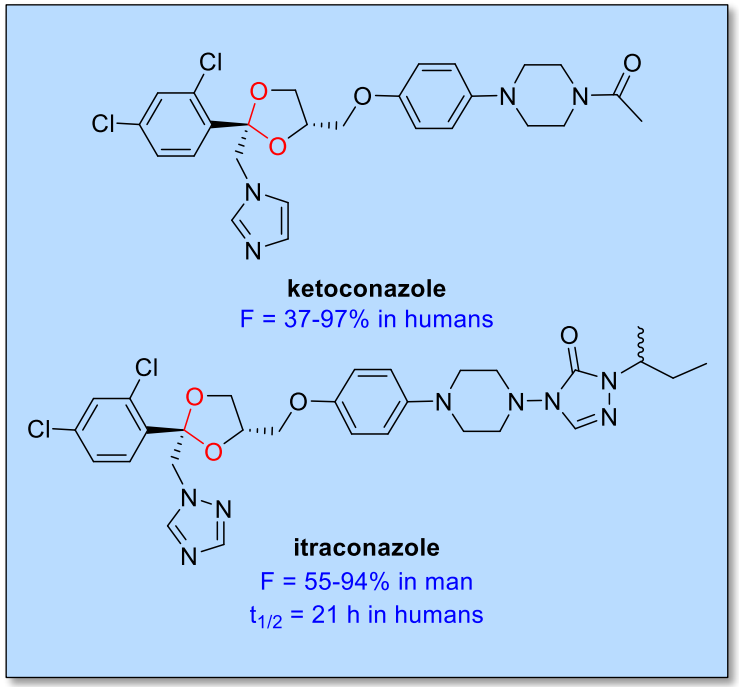
- Cannabinoid receptor 1 inverse agonists
- Lead pyridine-based compound unstable in weakly acidic media
  - pyridine *N* atom may contribute to hydrolysis
- Cl, F phenyl substituents improved chemical & metabolic stability
  - reduces carbenium ion stabilization
- Replacing pyridine N with C-F enhanced stability
  - known isostere
- 2,4-dichloro & fluoro substitution
  - increased lipophilic interactions with CB1R binding pocket
- Significant reduction in body weight gain in DIO rat model
  - PO administration



L. Alig *et al.*, *J. Med. Chem.*, 2008, **51**, 2115-2127

Stabilizing Ketals: Introduction of a Proximal Basic Amine

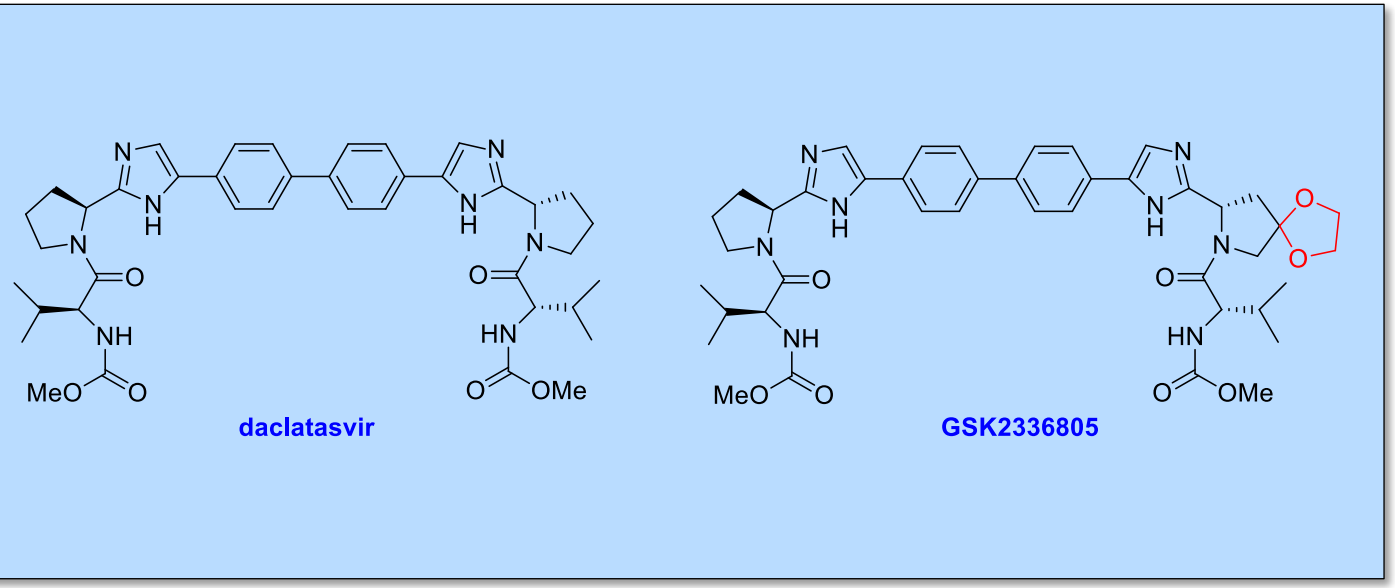




- Amino sugars are more resistant to acid hydrolysis than neutral sugars
  - *N* protonation reduces propensity for 2nd protonation at O
  - decosamine & cladinose in clarithromycin are differentiated
- Morpholine acetals are resistant to acid degradation
  - despite milder basicity of *N* atom
  - aprepitant is an acyclic acetal

- Conazole ketals stabilized by proximal basic imidazole & triazole
  - ketal is resistant to chemical degradation

Spiro Dioxolane in HCV NS5A Inhibitors



	daclatasvir	GSK2336805
pEC_{50} WT GT-1a	10.4 pM	10.4 pM
pEC_{50} WT GT-1b	11.3 pM	11.1 pM
pEC_{50} WT GT-1b L28V	11.4 pM	11.5 pM
pEC_{50} WT GT-1b L31V	9.9 pM	10.6 pM
pEC_{50} WT GT-1b Y93H	5.5 pM	10.6 pM
rat F	50%	13%
dog F	38%	51%
cynomolgus monkey F	67%	13%
$t_{1/2}$ in humans	12-15 h	8-10 h

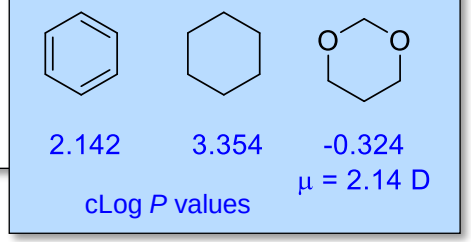
- Comparable potency to DCV toward wild type and mutant replicons
- Stable in dog, monkey and human hepatocytes:
  - $t_{1/2}$ >360 min
- GSK2336805 advanced into Phase 1 clinical trials
  - parent accounted for >95% of total drug-related material in human plasma extracts
- No appreciable hydrolysis to keto-daclatasvir was observed
  - not a prodrug of keto-daclatasvir

W.S. Kazmierski *et al*., *J. Med. Chem*., 2014, **57**, 2058-2073; D.A. Wilfret *et al*., *Antimicrob. Agents Chemother.,* 2013, **57**, 5037-5044

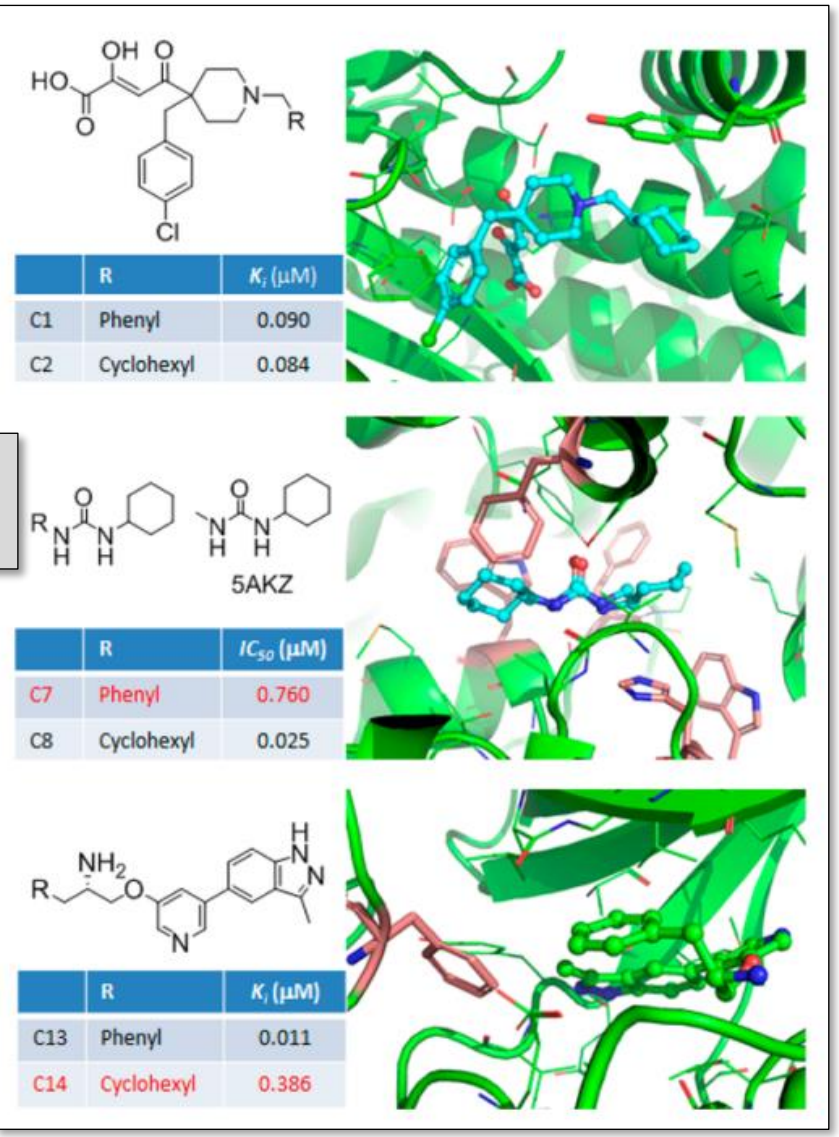
Cyclohexyl & 1,3-Dioxane as a Phenyl Isostere

- **Phenyl rings** are key pharmacophoric elements in drugs & candidates
  - most prevalent ring in marketed drugs
  - 10-fold more prevalent than 2nd ring - pyridine
- Frequently associated with π-π stacking interactions
- Matched pairs analysis: phenyl with cyclohexane
  - sampled the Merck, Amgen and BindingDB databases
    - 11021, 1341 and 2468 matched pairs, respectively
- For 36-45%, potency within 2-fold
  - for 25-39%, Ph ≥2-fold more potent
  - for 25-30%, cyclohexyl ≥2-fold more potent
- Examined examples in each category
  - only where X-ray cocrystal data available
  - phenyl & cyclohexyl can engage in similar types of stacking interactions
  - challenges a long-held assumption
- Replacing a Ph with **cyclohexyl** will increase Fsp^3
  - also increases Log *P* by ~0.5 unit
  - other adjustments may be required
- Carbohydrates engage in C-H to π interactions
  - polarized, electropositive C−H bonds due to proximal *O*
  - engage electron rich aromatic rings – e.g. Trp
  - replacing Ph with a dioxane reduces cLog *P* by 2.5 units

$$Fsp^3 = \frac{\#\ of\ sp^3\ C\ atoms}{total\ C\ count}$$

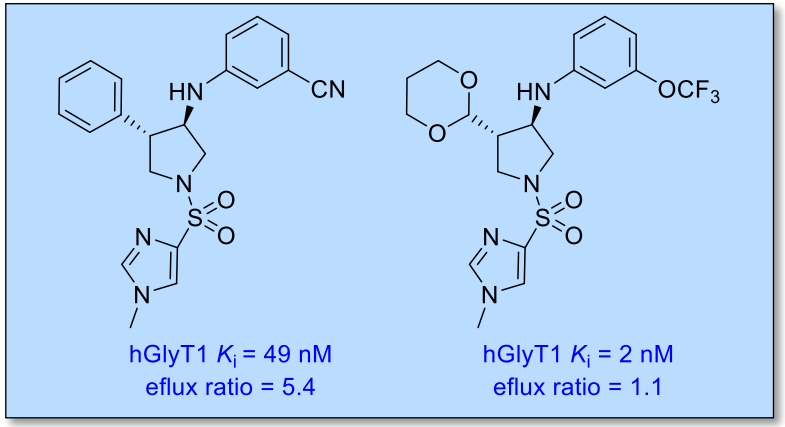


Top: Ph & Cy π stack
Middle: Cy >10x Ph
Bottom: Ph >10x Cy



H. Gunaydin & M.D. Bartberger, *ACS Med. Chem. Lett.*, 2016, **7**, 341-344; D.N. Woolfson *et al., J. Am. Chem. Soc*., 2015, **137**, 15152-15160; L.L. Kiessling & R.C. Diehl, *ACS Chem. Biol.* 2021, **16**, 1884–1893

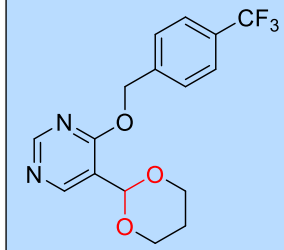
1,3-Dioxanes as Phenyl Replacements



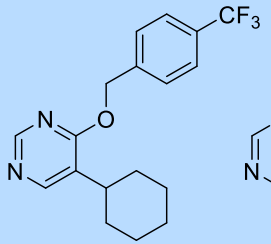
hGlyT1 K_i = 49 nM
eflux ratio = 5.4

hGlyT1 K_i = 2 nM
eflux ratio = 1.1

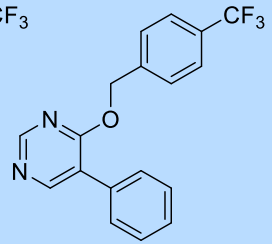
- Glycine transporter (GlyT1) inhibitors
- Dioxane substituted effectively for Ph
  - 25x potency increase; lower Log *P*
  - orally bioavailable
  - reduced efflux ratio, CNS penetrant



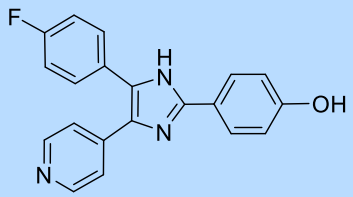
benzpyrimoxan
insecticide



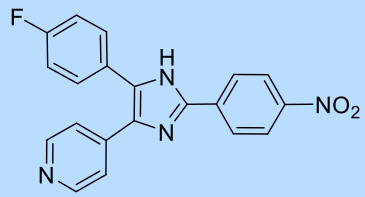
poorer residual activity



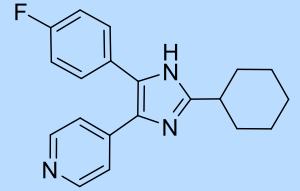
synthesized but no data provided



SB-2021901
p38 MAP kinase inhibitor
IC_{50} = 50 nM

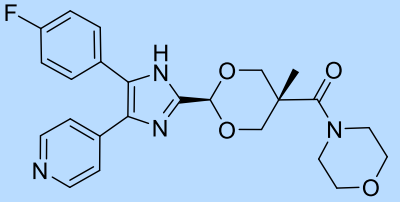


PD-169316
p38 MAP kinase inhibitor
IC_{50} = 89 nM



p38 MAP kinase inhibitor
IC_{50} = 70 nM

RPR201227A
p38 MAP kinase inhibitor
IC_{50} = 44 nM



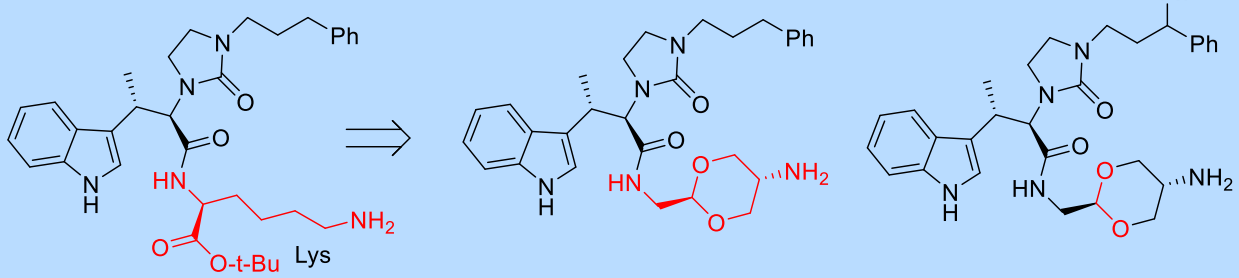
RPR200765A
p38 MAP kinase inhibitor
IC_{50} = 50 nM

- p38 MAP kinase inhibitors
  - spliceosome modulators with potential as anticancer agents
- Limited solubility of leads hindered formulation
  - cyclic acetal improved solubility by >50-fold
  - comparable *in vitro* and *in vivo* activity
  - stable in acid: pyridine, imidazole protonation; imidazole electron withdrawal
- Dioxane is a mimic of a phenyl & cyclohexyl ring in this context
  - N-H: weakly basic - cpK_a = 7.7
  - phenol isostere, aniline isostere?

Y. Wang *et al., J. Med. Chem.*, 2018, **61**, 7486-7502; C.R.J. Stephenson *et al.,* ACS *Med. Chem. Lett.*, 2020, **11**, 1785–1788
I.M. McClay *et al., Bioorg. Med. Chem.*, 2001, **9**, 537-554; D.N. Woolfson *et al., J. Am. Chem. Soc*. 2015, **137**, 15152-15160; E. Satoh *et al., J. Pestic. Sci.*, 2021, **46**, 109–114

5-Amino-1,3-Dioxane & Developability Parameters

Somatostatin Agonists



hSSTR-2 K_i = 3.6 nM
F = 5% in dogs

hSSTR-2 K_i = 18 nM
F = 19% in dogs

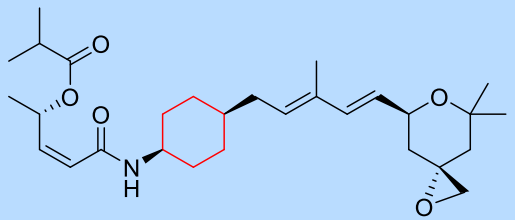
hSSTR-2 K_i = 8.5 nM
F = 64% in dogs

- Somatostatin agonists – inhibitory hormone
  - selective for the SSTR-2 receptor
- 2-Aminomethyl-5-amino-1,3-dioxane explored as a Lys surrogate
  - less basic amine than Lys
  - devoid of the ester group
- Designed to improve absorption
  - F increased from 5% to 19%
- Incorporation of additional phenyl ring restored potency
  - further improved %F to 64%

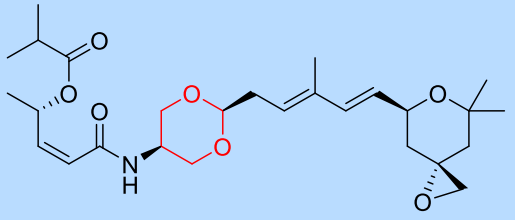
First application of 5-amino-1,3-dioxane in medicinal chemistry
- acetal moiety stabilized by proximal basic amine (cpK_a = 7.7)

- Sudemycins – natural products
  - mRNA splicing modulators
  - offer potential as anticancer agents
- Limited solubility hindered formulation
  - synthetic modifications explored
  - cyclic acetal improved solubility by >50-fold
- Comparable *in vitro* and *in vivo* activity
  - 1,3-dioxane acts as an effective mimic of cyclohexane

Sudemycins



Sudemycin C1
Jeko-1 cytotoxicity IC_{50} = 120 nM
solubility in H_2O & PBS <1 μM

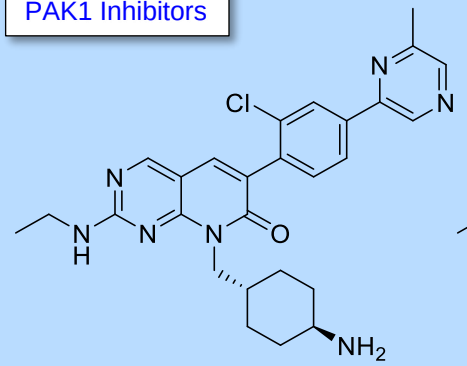


Sudemycin E
Jeko-1 cytotoxicity IC_{50} = 150 nM
solubility in PBS = 47 μM

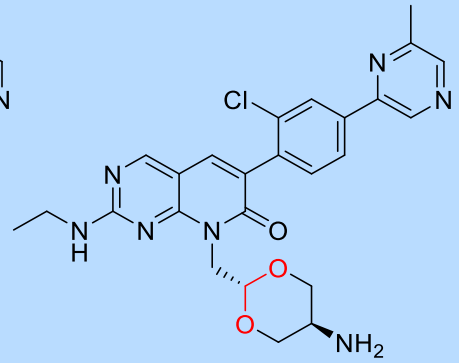
A. Pasternak *et al*., *Bioorg. Med. Chem. Lett*., 1999, **9**, 491-496; T.R. Webb *et al*., *J. Med. Chem*., 2009, **52**, 6979-6990

5-Amino-1,3-dioxane: Reducing hERG Inhibition

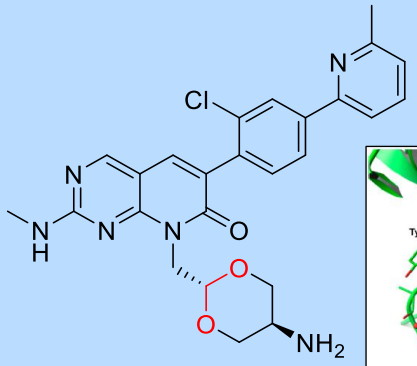
PAK1 Inhibitors



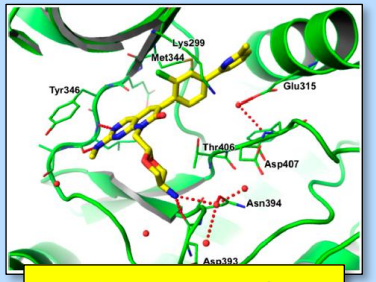
PAK1 K_i = 1.9 nM
cpK_a = 10.4
cLog P = 4.5
P_{app} = 0.4 x 10^{-6} cm/s
hERG inhibition = 58% @ 10 μM



PAK1 K_i = 8.0 nM
cpK_a = 7.7
cLog P = 2.4
P_{app} = 1.7 x 10^{-6} cm/s
hERG inhibition = 11% @ 10 μM



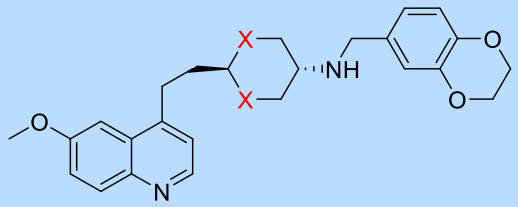
G-5555
PAK1 K_i = 3.7 nM
cpK_a = 7.7
cLog P = 2.9
P_{app} = 2.4 x 10^{-6} cm/s
hERG inhibition = 45% @ 10 μM
F = 80% (mice); 72% (monkeys)



X-ray cocrystal
di-equatorial disposition

PAK1: p21 activating protein kinase

Bacterial Topoisomerase 1 Inhibitors



X = CH_2
cpK_a = 9.5
hERG IC_{50} = 0.26 μM

X = O
cpK_a = 7.2
hERG IC_{50} = 5.1 μM
S. aureus MIC = 0.25-1 μg/mL

- Bacterial topoisomerase inhibitors
  - problematic hERG inhibition with cyclohexane
- 1,3-Dioxane reduced cpK_a of amine
  - ~20-fold lower hERG inhibition

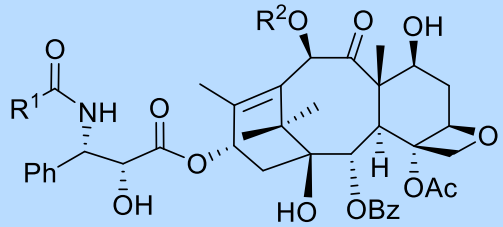
- Cyclohexylamine-based PAK1 inhibitor associated with hERG inhibition
  - cpK_a = 10.4
- Cyclic acetal simultaneously reduced cLog P (Δ = 2.1) and cpK_a (Δ = 2.7)
  - increased membrane permeability by 4-fold
  - reduced hERG inhibition by 5-fold
- Stable at pH = 0, 1, 2 for 24 hours
  - protected by protonation of the mildly basic amine

"1,3-dioxanes are not commonly found in active pharmaceutical agents due to their perceived instability"

Dioxane an effective mimic of cyclohexane
- with advantages

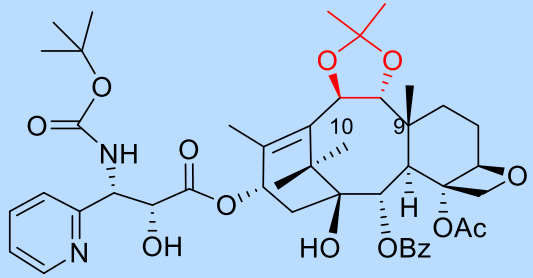
C.O. Ndubaku *et al*., *ACS Med. Chem. Lett*., 2015, **6**, 1241-1246; M.J. Mitton-Fry *et al., Bioorg. Med. Chem. Lett.,* 2018, **28**, 2477-2480; *ACS Med. Chem. Lett*., 2020, **11**, 2446-2454

Taxane 9,10-Ketal and Acetal

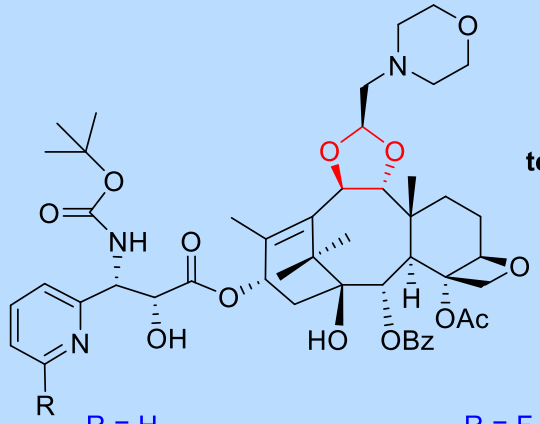


paclitaxel: R^1 = Ph, R^2 = Ac
GI_{50} (PC-6) = 1.27 ng/mL
GI_{50} (PC-12) = 539 ng/mL

docetaxel: R^1 = *t*-BuO, R^2 = H
GI_{50} (PC-6) = 1.48 ng/mL
GI_{50} (PC-12) = 42.2 ng/mL



GI_{50} (PC-6) = 0.33 ng/mL
GI_{50} (PC-12) = 0.15 ng/mL

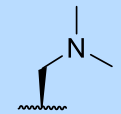


R = H
GI_{50} (PC-6) = 0.29 ng/mL
GI_{50} (PC-12) = 0.14 ng/mL

R = F
GI_{50} (PC-6) = 0.31 ng/mL
GI_{50} (PC-12) = 0.11 ng/mL

R = OMe
GI_{50} (PC-6) = 0.07 ng/mL
GI_{50} (PC-12) = 0.14 ng/mL

R = OH (metabolite)
GI_{50} (PC-6) = 0.02 ng/mL
GI_{50} (PC-12) = 2.66 ng/mL

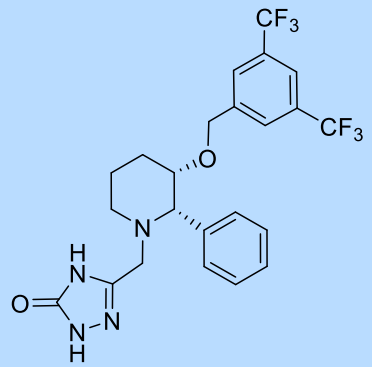


tesetaxel (2-F-pyridine)
PIII clinical trials
orally bioavailable

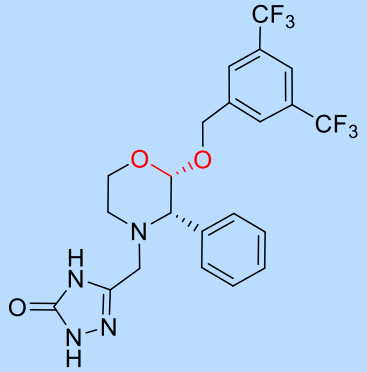
- Paclitaxel/docetaxel
  - poor oral F due to low solubility
- Acetone-based ketal enhanced potency
  - metabolism of the pyridine ring blocked with F, Cl, or OMe substituent
- Incorporation of morpholine & Me_2N-based acetals contributed to better solubility
  - resulted in orally active compounds
  - tesetaxel well-absorbed, long $t_{1/2}$
    - advanced to PIII clinical trials

T. Ishiyama *et al*., *Bioorg. Med. Chem. Lett.,* 2002, **12**, 1083-1086; 2002, **12**, 2815-2819
Y. Takeda *et al*., *Bioorg. Med. Chem. Lett.,* 2003, **13**, 185-190; 2004, **14**, 3209-3215; *Bioorg. Med. Chem*., 2003, **11**, 4431-4447

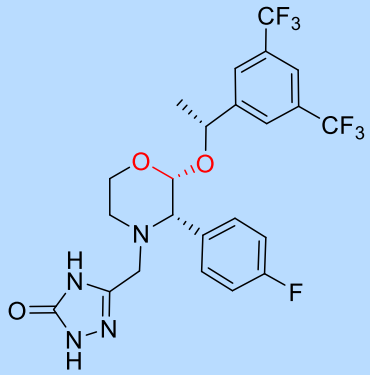
Morpholine-Based Acyclic Acetals in NK1 Antagonists



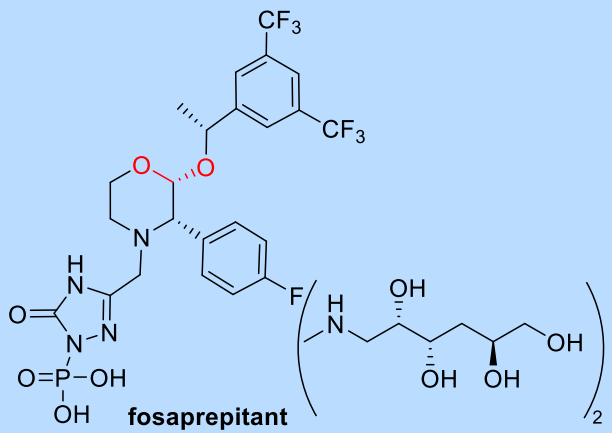
L-742691
pK_a = 5.3
hNK1 IC_{50} = 0.05 nM
Ca^{2+} binding IC_{50} = 13 μM
SPIDER ID_{50} = 0.037 mpk



L-742694
pK_a <3
hNK1 IC_{50} = 0.09 nM
Ca^{2+} binding IC_{50} = 12 μM
SPIDER ID_{50} = 0.009 mpk



aprepitant
hNK1 IC_{50} = 0.09 nM
Ca^{2+} binding IC_{50} >1 μM

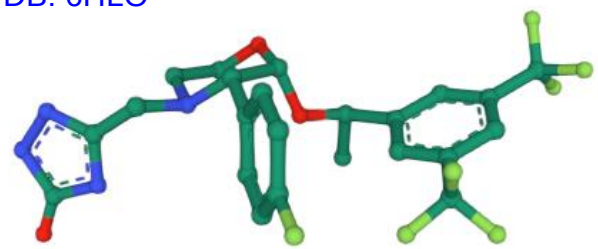


fosaprepitant
prodrug for IV

Emend®
prevents chemotherapy-induced nausea & vomiting

- Morpholine analogs are stable in simulated gastric fluid
- Piperidine → morpholine reduces amine pK_a value by >2
- Morpholine acetal increased potency *in vivo* by 4-fold
  - ID_{50} ranges from 0.037 to 0.009 mpk
- *O*-benzyl adopts axial disposition in cocrystal structure
  - stabilized by the anomeric effect
- Fosaprepitant dimeglumine
  - a phosphate prodrug for IV administration

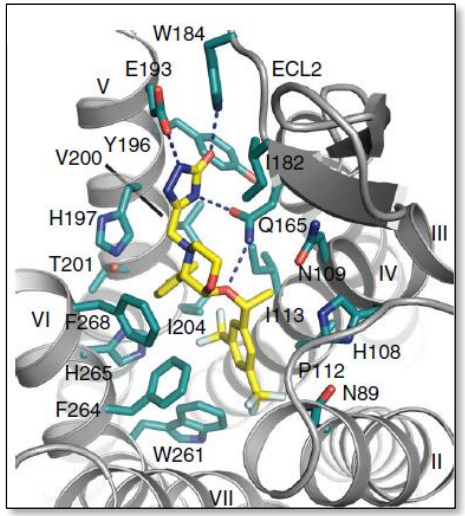
PDB: 6HLO

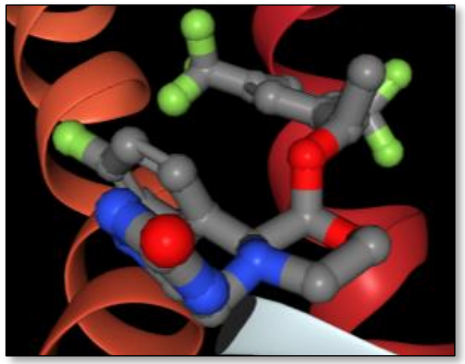


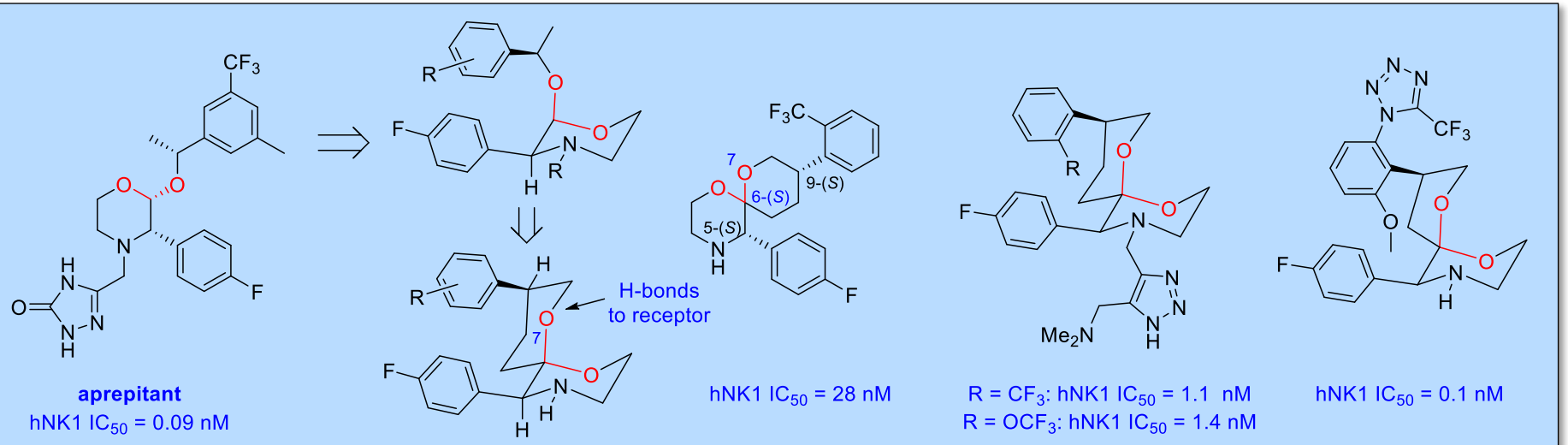
Ca^{2+} binding = displacement of [^{3}H]-diltiazem from rabbit skeletal muscle Ca^{2+} channel

J.J. Hale *et al., J. Med. Chem*., 1996, **39**, 1760-1762; 1998, **41**, 4607-4614; T. Ladduwahetty *et al*., *J. Med. Chem*., 1996, **37**, 2907-2914; S. Chen *et al., Nature Commun*., 2019, **10**,article # 638

Morpholine-Based Spirocyclic Ketals in NK1 Antagonists







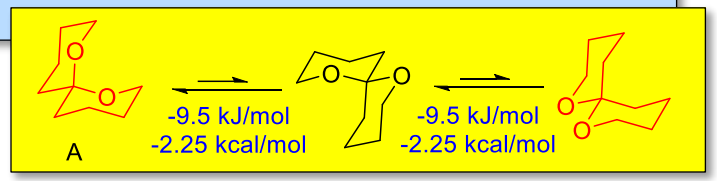
aprepitant
hNK1 IC_{50} = 0.09 nM

hNK1 IC_{50} = 28 nM

R = CF_3: hNK1 IC_{50} = 1.1 nM
R = OCF_3: hNK1 IC_{50} = 1.4 nM

hNK1 IC_{50} = 0.1 nM

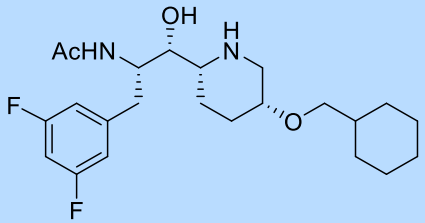
2 reinforcing anomeric effects:
both C–O bonds are antiperiplanar to an *O* lone pair in the spiro ring
-4.5 kcal/mol lower in energy than the worst conformer



- Intramolecular Ph-Ph interaction stabilizes aprepitant in the bound conformation
  - edge-to-face or face-to-face
- Spirocyclic ketal A offers conformational rigidity due to 2 reinforcing anomeric effects
  - (5*S*,6*S*,9*S*-) configuration provides optimal orientation of the 2 aryl rings
  - maintains the key H-bond interaction between Gln_{165} side chain NH of the receptor & O-7
- The (5*S*,6*S*,9*S*-) diastereomer is significantly more active than the other 3 diastereomers
  - both compounds penetrated the CNS of gerbils after IV administration; no PO data

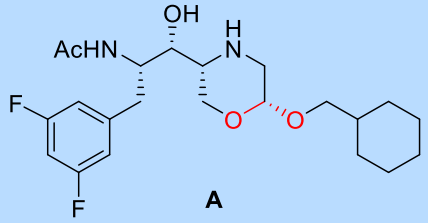
E.M. Seward *et al*., *Bioorg. Med. Chem. Lett*., 2002, **12**, 2515-2518; P. Deslongchamps *et al., Can. J. Chem*. 1981, **59**, 1105-1121
A. Plückthun *et al., Nature Commun*., 2019, **10**, article # 17; S. Chen *et al*., *Nature Commun*., 2019, **10**, article # 638

Morpholine-Based Acetals in BACE1 Inhibitors



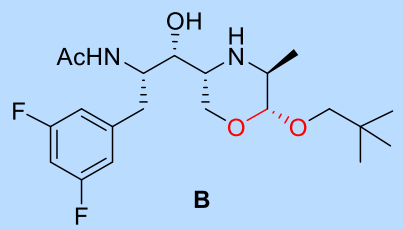
BACE1 cell IC_{50} = 0.53 μM
cpK_a = 8.6
brain exposure = 87 mg/g
B/P ratio = 0.07

Δ cpK_a = 1.9



A

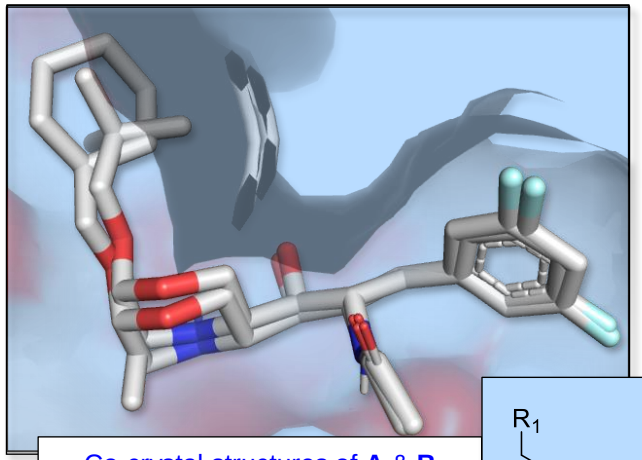
BACE1 cell IC_{50} = 0.48 μM
cpK_a = 6.7
brain exposure = 427 mg/g
B/P ratio = 0.42



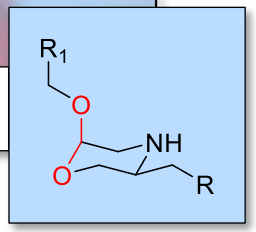
B

BACE1 cell IC_{50} = 0.09 μM
cpK_a = 6.9
brain exposure = 739 mg/g
B/P ratio = 0.38

brain exposure, B/P ratio: 1 h after 30 mpk, SC (mice)



Co-crystal structures of **A** & **B** bound to the BACE1 active site

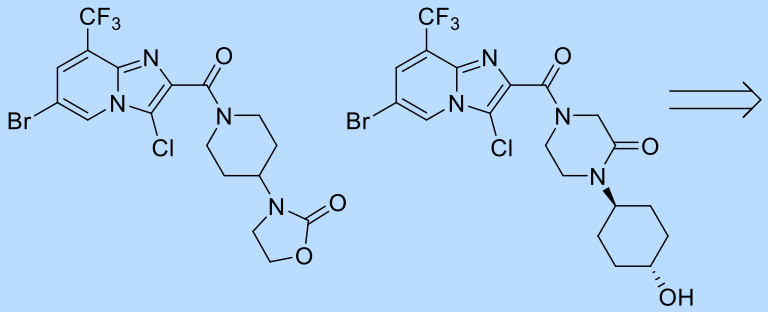


- Piperidine and morpholine adopt similar chair conformations
  - NMR and X-ray analyses
  - alkoxy substituent oriented with an axial disposition
  - reinforced by the anomeric effect in the morpholine analogue
- Piperidine → morpholine reduces basicity
  - cpK_a reduced by 1.9
- Morpholine acetal improved brain exposure by 5-fold
  - 7-fold increase in B/P ratio
  - Me enhanced potency 6-fold

"While 2-alkoxymorpholines are unusual cores in drug discovery, they are stable compounds that have produced marketed drugs"

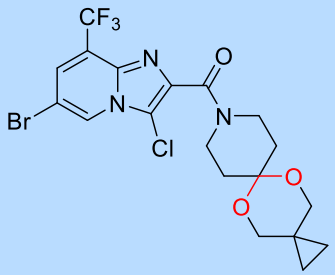
A.B. Bueno *et al.*, *J. Med. Chem.*, 2017, **60**, 9807-8920

1,3-Dioxane & Conformational Mimicry of a Carbamate

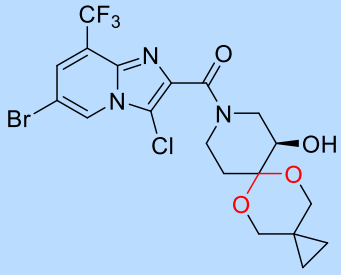


EC_{50} HCV GT-1a = 31 nM
EC_{50} HCV GT-1b = 46 nM

EC_{50} HCV GT-1a = 0,3 nM
EC_{50} HCV GT-1b = 2.0 nM



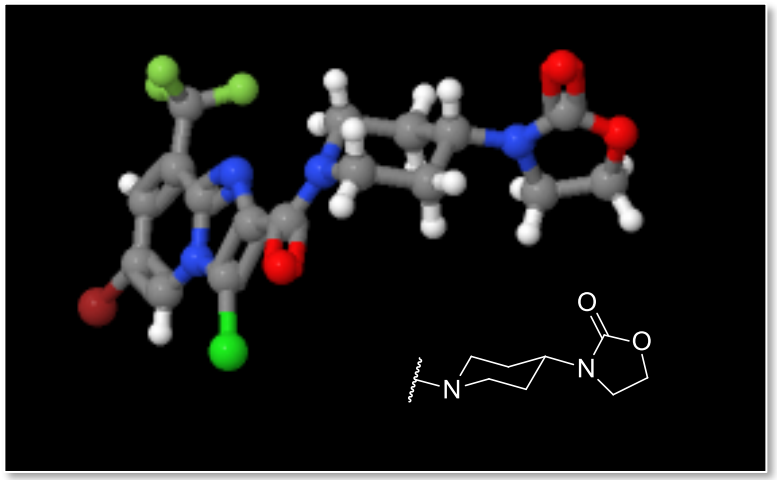
EC_{50} HCV GT-1a = 9.0 nM
EC_{50} HCV GT-1b = 4.1 nM
human $t_{1/2}$ = 30 min
rat $t_{1/2}$ < 15 min
F = 29% in rats

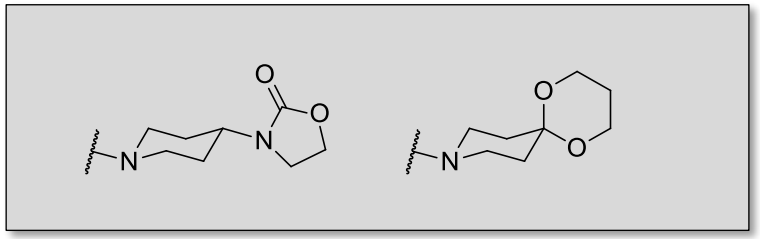


EC_{50} HCV GT-1a = 1.5 nM
EC_{50} HCV GT-1b = 1.2 nM
human $t_{1/2}$ = 50 min
rat $t_{1/2}$ = 28 min
F >100% in rats

HCV NS4B Inhibitors

$t_{1/2}$ in human & rat hepatocytes

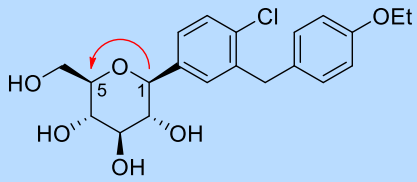




- X-ray structure of the lead compound
  - orthogonal orientation between piperidine & oxazolidinone rings
- Spiro ketal was designed to constrain both rings in perpendicular planes
  - mimic the oxazolidinone geometry
- One ketal oxygen atom acts as a H-bond acceptor
  - mimics the carbamate C=O
- Excellent oral bioavailability in the rat
  - hydroxy substituent increases metabolic stability, PK profile

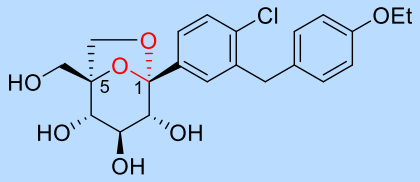
V. W.-F. Tai *et al., Bioorg. Med. Chem. Lett.*, 2014, **24**, 2288-2294

Spirocyclic Ketals in SGLT2 Inhibitors: 2 Designs

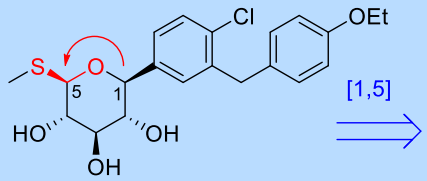


dapagliflozin
hSGLT2 IC_{50} = 2.4 nM
hSGLT1 IC_{50} = 392 nM

[1,5]

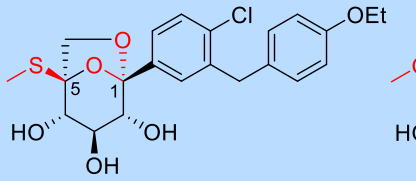


ertugliflozin
hSGLT2 IC_{50} = 0.88 nM
hSGLT1 IC_{50} = 2.0 μM
$t_{1/2}$ = 11-17 h (human)
F = 70-90% (human)

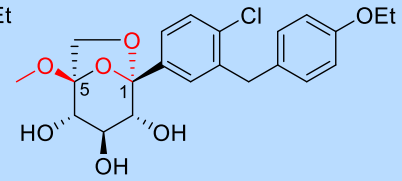


sotagliflozin
hSGLT2 IC_{50} = 1.5 nM
hSGLT1 IC_{50} = 35 nM
dual inhibitor

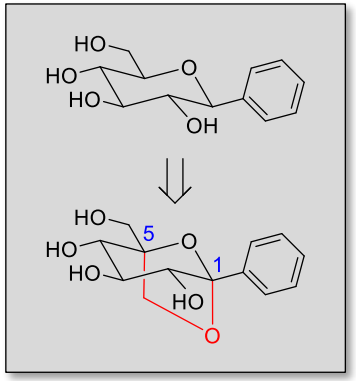
[1,5]



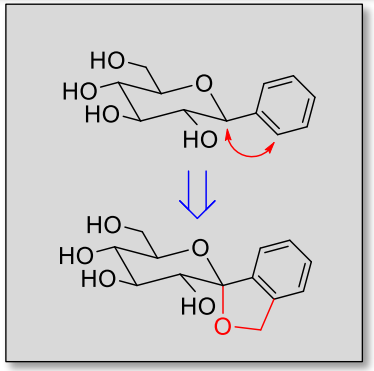
hSGLT2 IC_{50} = 14 nM
hSGLT1 IC_{50} = 450 nM

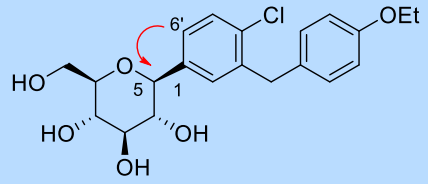


HSK0935
hSGLT2 IC_{50} = 1.3 nM
hSGLT1 IC_{50} = 1,100 nM
$t_{1/2}$ = 3.6 (rats)
F = 76% (rats)



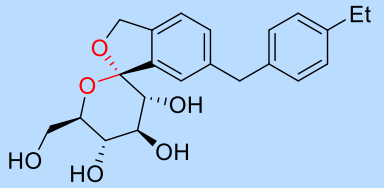
alternative spirocycle designs





dapagliflozin
hSGLT2 IC_{50} = 2.4 nM
hSGLT1 IC_{50} = 392 nM

[1,6']



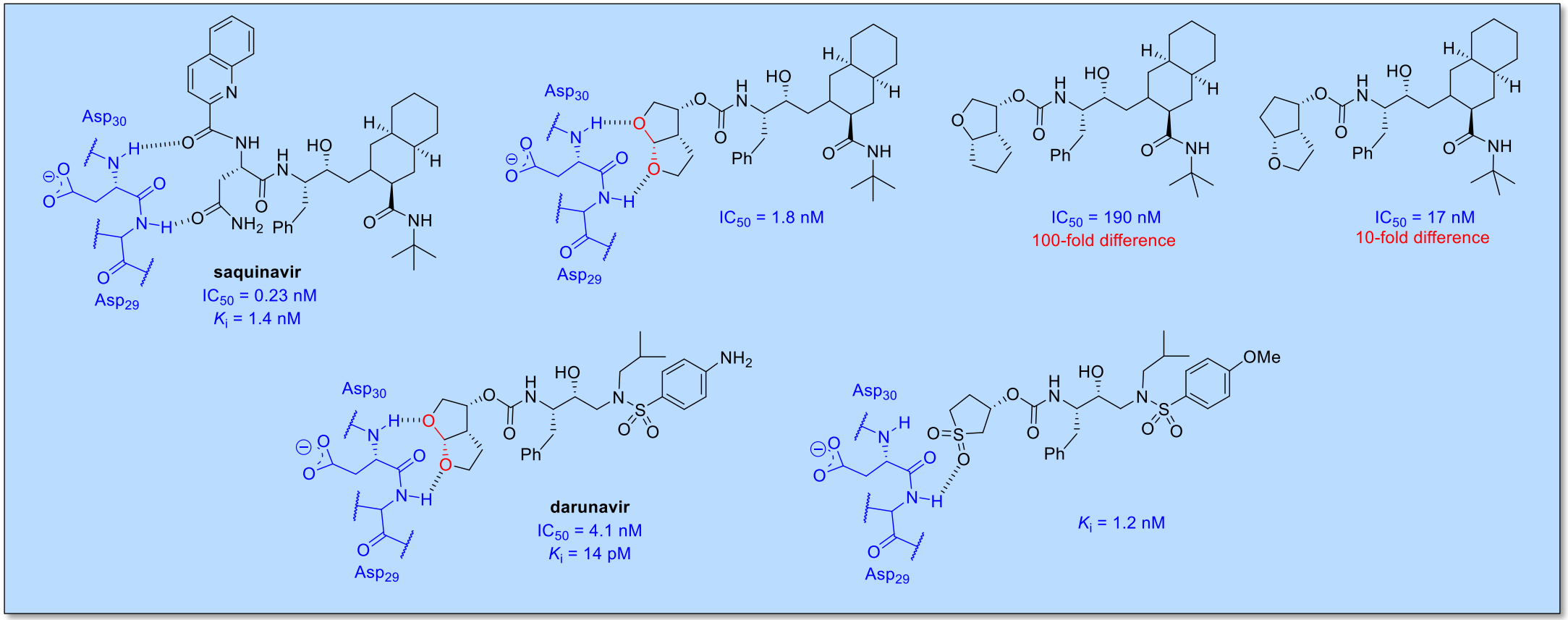
tofogliflozin
hSGLT2 IC_{50} = 2.9 nM
hSGLT1 IC_{50} = 8,400 nM
F = 75% (mouse); 85% (monkey)

- 1,5-Cyclized ketal positively impacts both potency and selectivity
  - enhances SGLT2 inhibition while weakening SGLT1 inhibition
- Cyclization of sotagliflozin & optimization
  - transformed a dual SGLT1 & 2 inhibitor into a selective SGLT2 inhibitor
  - SCH_3 to OCH_3 enhances SGLT2 inhibition 10x; reduces SGLT1 inhibition 2x

- SGLT2 inhibitor lowest energy conformation
  - glycoside & phenyl ring are orthogonal
- Reproduced by 1,6'-cyclized spiroketal moiety
  - enhanced selectivity for SGLT2 by 20x

V. Mascitti *et al.*, *J. Med. Chem.*, 2011, **54**, 2952-2960; *Med. Chem. Commun.*, 2013, **4**, 101-111; Y. Li *et al.*, *J. Med. Chem.*, 2017, **60**, 4173-4184
Y. Ohtake *et al.*, *J. Med. Chem.*, 2012, **55**, 7828-7840; B. Lv *et al.*, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 6877-6881

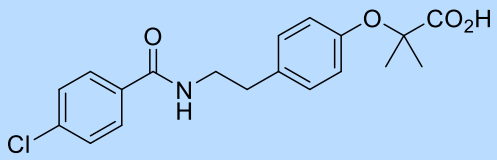
Bis-THF: P2 Element for HIV-1 Protease Inhibitors



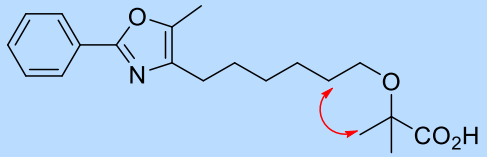
- Incorporation of bis-THF eliminates 2 amide moieties (total of 3 N-Hs) in saquinavir
  - reduces MW: 669 to 547
  - lowers lipophilicity: cLog *P*: 5.08 to 3.2
- Two acetal O atoms act as H-bond acceptors engaging the backbone NH's of Asp_{30} and Asp_{29}
  - bis-THF moiety may be viewed as a bioisostere of a cyclic sulfone

A.K. Ghosh, *J. Med. Chem.*, 2009, **52**, 2163-2175; I.T. Weber *et al., J. Med. Chem.,* 2013, **56**, 1074-1083
A.K. Ghosh *et al.*, *J. Med. Chem.*, 2017, **60**, 4267-4278; *Acc. Chem. Res.*, 2008, **41**, 78-86; *ChemMedChem,* 2006, **1**, 939-950

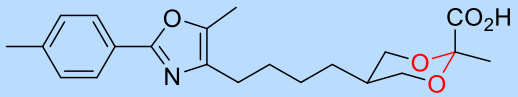
1,3-Dioxane Acid in Fibrates: Selectivity, Conformation



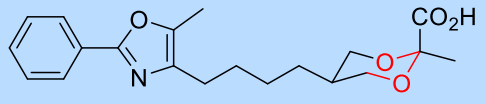
bezafibrate
lipid-lowering agent
hPPAR-α EC_{50} = 30 μM
hPPAR-γ EC_{50} = 100 μM
hPPAR-δ EC_{50} = 100 μM



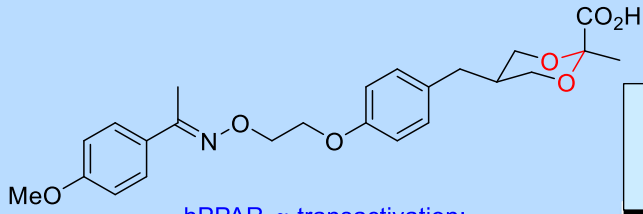
hPPAR-α EC_{50} = 0.3 μM
hPPAR-γ EC_{50} = 0.3 μM
hPPAR-δ EC_{50} = 30 μM



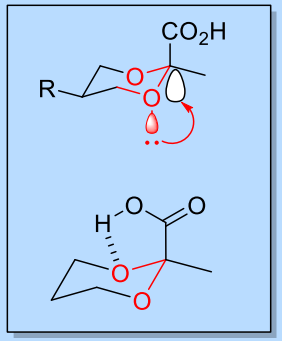
NS-220
hPPAR-α EC_{50} = 0.01 μM
hPPAR-γ 31% max response (10 μM)
hPPAR-δ 7% max response (10 μM)

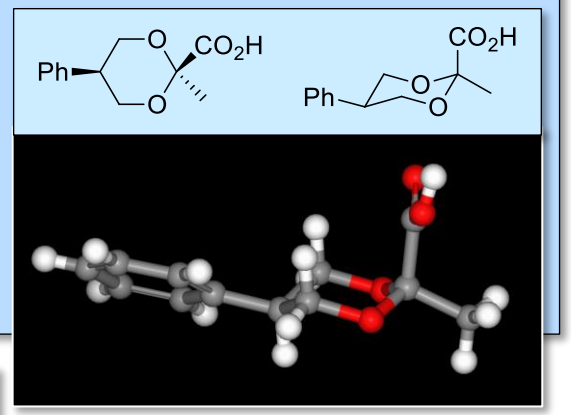


hPPAR-α EC_{50} = 0.3 μM
hPPAR-γ EC_{50} = 100 μM
hPPARδ 0% max response (10 μM)



hPPAR-α transactivation:
15-fold induction @ 10 μM



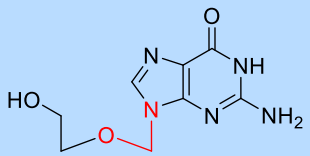


- Alkyl analog of bezafibrate 100-fold more potent
  - cyclization with incorporation of dioxane maintained potency
  - enhanced selectivity for PPARα by reducing PPARδ affinity
- CO_2H moiety adopted an axial disposition
  - stabilized by a general anomeric effect between O lone pairs and σ* of CO_2H
  - dipole alignment may contribute
  - *trans* ester hydrolyzes faster than the *cis* isomer

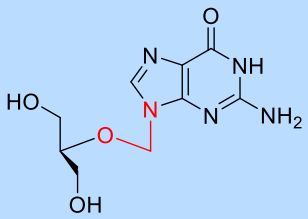
T. Asaki *et al., Bioorg. Med. Chem.,* 2008, **16**, 981-994; *Bioorg. Med. Chem. Lett.,* 2008, **18**, 2128-2132
C. Tschierske *et al., Tetrahedron*, 1989, **45**, 6987-6998; T. Harabe *et al., Tet. Lett.*, 2007, **48**, 1443-1446; *Tetrahedron*, 2009, **65**, 4044-4052; CDC DOI: 10.5517/ccdc.csd.cc29ff28

N,O-Aminal & *N,N*-Aminal Derivatives

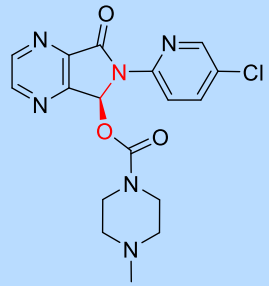
(*N,O*)-Aminals in Marketed Drugs & Preclinical Compounds



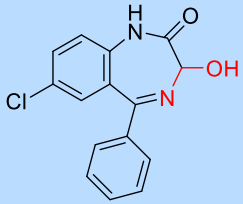
acyclovir
solublity = 2.5 mg/mL (pH 7.4)
F = 15%; $t_{1/2}$ = 2.7 h



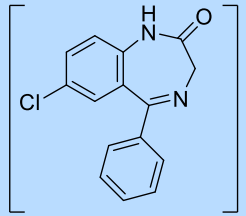
ganciclovir
solublity = 2 mg/mL (pH 7.4)
F = 9%; $t_{1/2}$ = 5.2 h



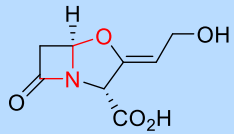
zopiclone (racemate)
eszopiclone (*S* enantiomer)
$t_{1/2}$ = 5 h
F = 80% in man



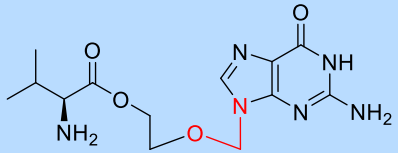
oxazepam
treatment of anxiety
and insomnia
$t_{1/2}$ = 5.8 h
F = 93%



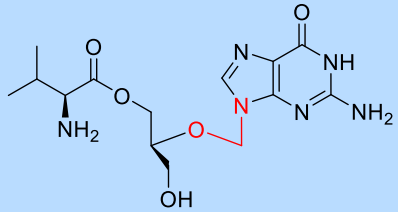
diazepam



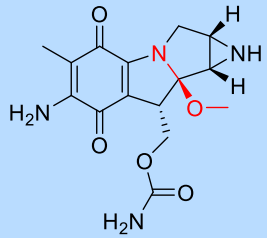
clavulanic acid
β-lactamase inhibitor



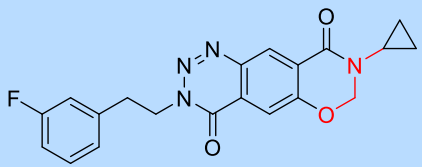
valacyclovir
solublity = 174 mg/mL (H_2O)
F = 54%



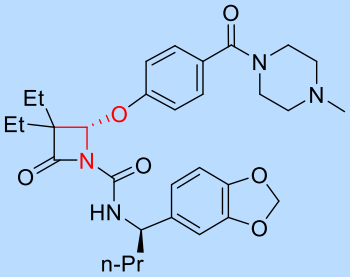
valganciclovir
solublity = 70 mg/mL (H_2O)
F = 65%



mitomycin C
antitumor
IV

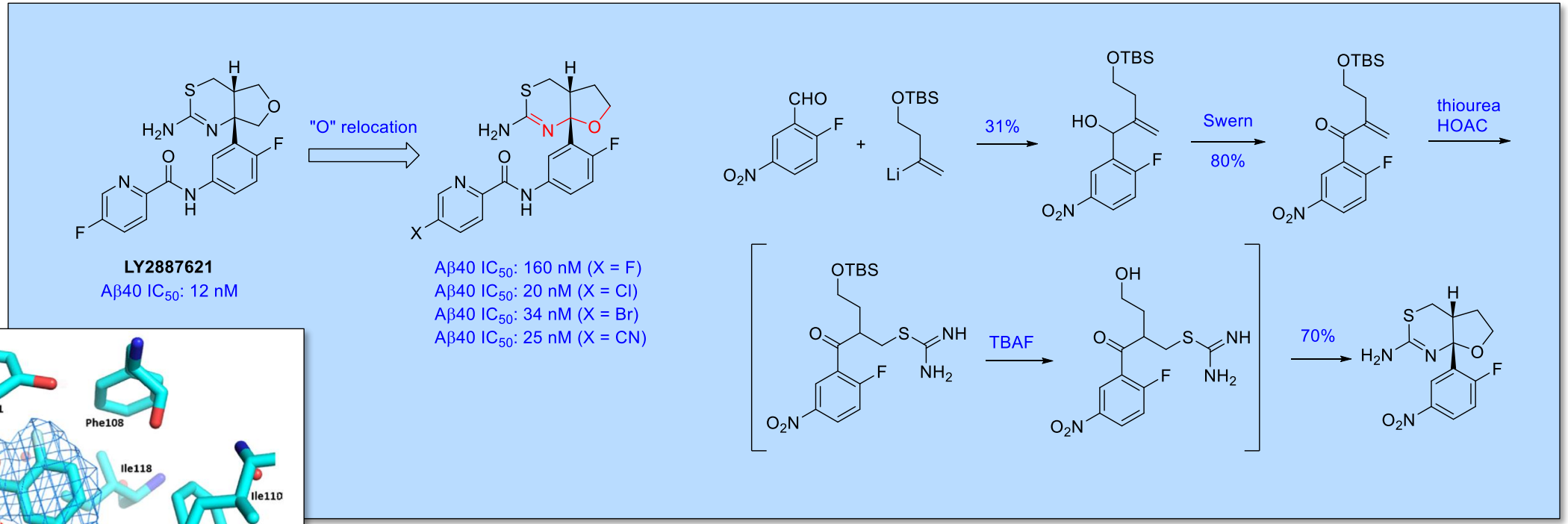


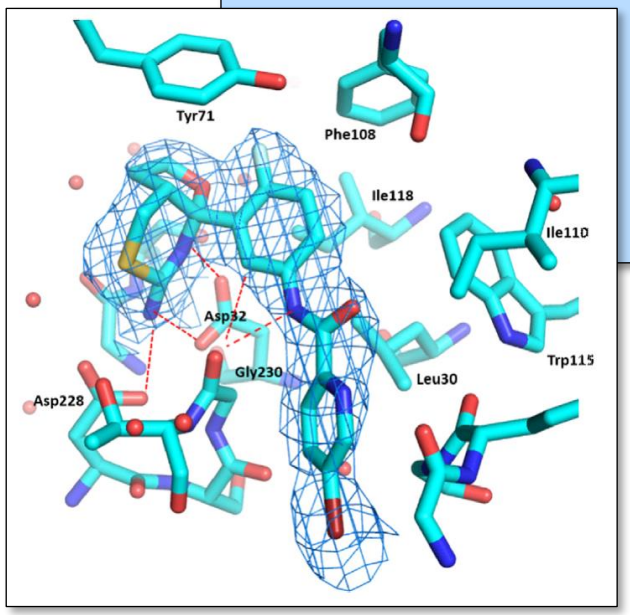
tulrampator, phase II
antidepressant
AMPA EC_{50} = 6.54 μM; E_{max} = 7.85 (rat)
AMPA EC_{50} = 7.08 μM; E_{max} = 6.87 (human)



L-694,458, DMP 777
polymorphonuclear leukocyte
elastase (PMNE) inhibitor
F = 39% (monkey); 65% (rat)
$t_{1/2}$ = 6 h (monkey)

(*N*,*O*)-Aminals in BACE1 Inhibitors

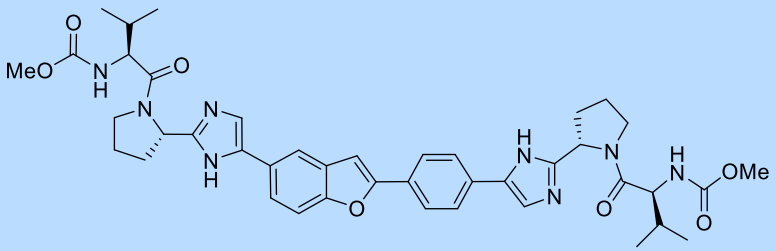




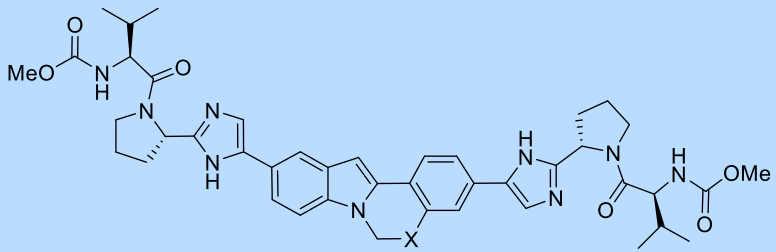
- Bicyclic aminal core readily prepared in 3 steps
  - in essence, topologically relocates the O atom
  - has impact on the basicity of the isothiourea moiety
- Co-crystal structure bound to BACE active site
  - showed good overlap with LY2887621
  - 13-fold less potent than LY2887621
- Bicyclic aminal is chemically and metabolically stable
  - stable in aqueous media pH 1–10 at 40°C for 24 h

Y.-J. Wu *et al., J. Org. Chem.*, 2016, **81**, 3386-3390; *Bioorg. Med. Chem. Lett.*, 2016, **26**, 5729-5731

(*N*,*O*)-Aminals in HCV NS5A Inhibitors

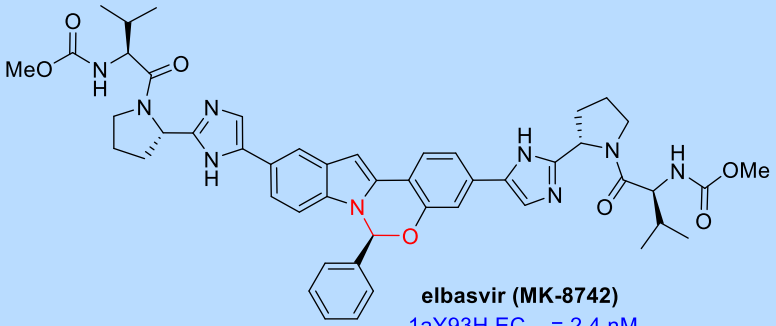


MK-4882
GT-1aY93H EC_{50} = 27 nM

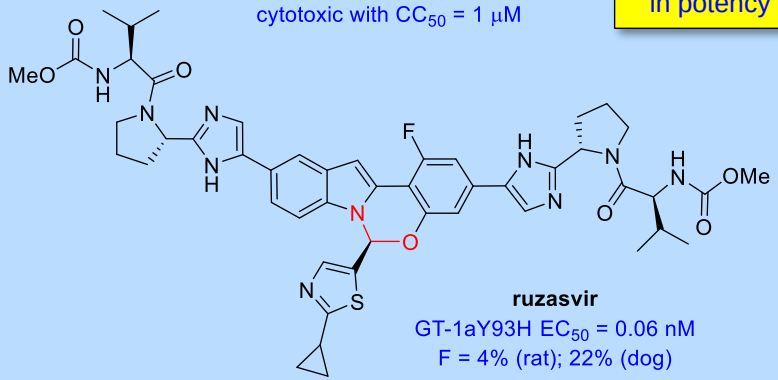


X = CH_2: GT-1aY93H EC_{50} = 170 nM
X = O: GT-1aY93H EC_{50} = 5 nM
cytotoxic with CC_{50} = 1 μM

34x increase in potency



elbasvir (MK-8742)
1aY93H EC_{50} = 2.4 nM
F = 9% (rat); 35% (dog);
17% (monkey); 32% (humans)

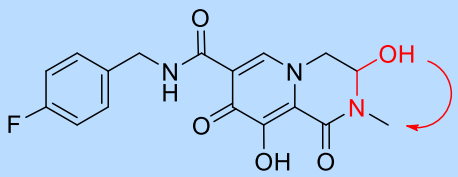


ruzasvir
GT-1aY93H EC_{50} = 0.06 nM
F = 4% (rat); 22% (dog)

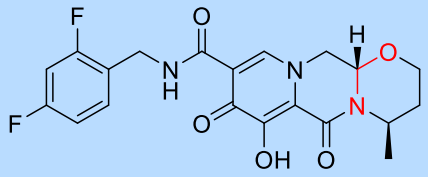
- Tetracyclic aminal system provided superior antiviral profile
- Potency: $–CH_2O$ > $–CH_2CH_2–$ by 30-fold
  - unsubstituted $–CH_2O–$ analogs cytotoxic;
  - no cytotoxicity with –CH(R)O– analogs
- Aminal linkage resistant to hydrolytic cleavage, even under harsh conditions
  - non-basic indole *N*
  - aryl-*O* atom resistant to protonation

C.A. Coburn *et al*., *ChemMedChem,* 2013, **8**, 1930-1940; W. Yu *et al*., *J. Med. Chem*., 2016, **59**, 10228-10243; L. Tong *et al*., *J. Med. Chem*., 2017, **60**, 290-306

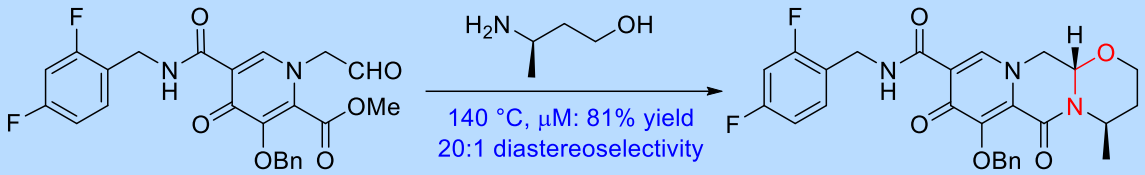
(*N*,*O*)-Aminals in HIV-1 Integrase Strand Transfer Inhibitors



8*S*: IC_{50} = 1.9 nM; PA IC_{50} = 81 nM
F = 79% (rat)
8*S*: IC_{50} = 2.2 nM; PA IC_{50} = 9.4 nM
F = 52% (rat)



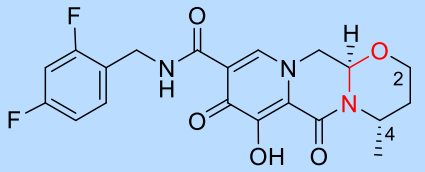
dolutegravir
IC_{50} = 1.7 nM
F = 34% (rat); 35% (dog); 25% (cyno)
$t_{1/2}$ = 14 h in humans



140 °C, μM: 81% yield
20:1 diastereoselectivity

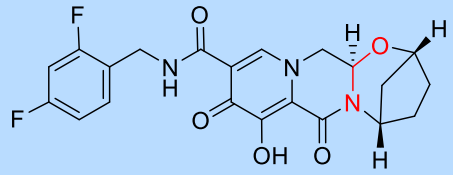
"We were initially concerned that the hemiaminal stability would be an issue, but no interconversion or chemical stability issues were observed with the purified isomers"

- Hemiacetal OH increases activity against resistant mutants
- Cyclic aminals used to overcome stability issue with hemi-aminal lead
  - enantiomers resolved: equipotent
  - stable entity with no interconversion
- 1:1 mixture obtained with 3-aminopropanol; stereoselective synthesis not available
  - stereochemical control with chiral substituted 3-aminopropan-1-ol
- Substituted oxazinane analogs retained good activity and PK properties

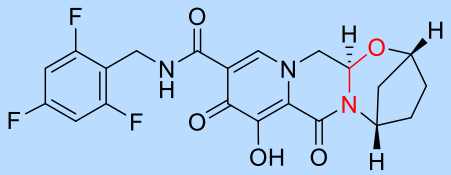


EC_{50} = 0.5 nM

[2,4]-ring closure ⇩



EC_{50} = 2.2 nM
G140S/Q148R fold shift = 3.4
PXR %Emax @ 15 μM = 5

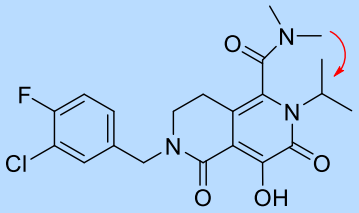


bictegravir
EC_{50} = 1.9 nM
G140S/Q148R fold shift = 2.0
PXR %Emax @ 15 μM = 18
F = 50% (rat); 28% (dog)
$t_{1/2}$ = 19 h in humans

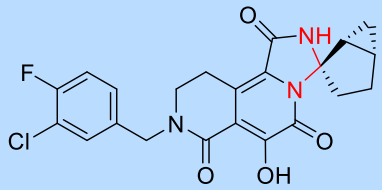
- [3.2.1]-bicyclic system associated with lower PXR activation
- Additional F atom on phenyl ring improved aqueous solubility
  - afforded bictegravir

T. Kawasuji *et al*., *J. Med. Chem*., 2013, **56**, 1124-1135; B.A. Johns *et al*., *J. Med. Chem.,* 2013, **56**, 5901-5916
Successful Strategies for the Discovery of Antiviral Drugs, M. Desai, N.A. Meanwell, Eds. *RSC Publishing*, Chapter 6; S.E. Lazerwith *et al*., *ASM Microbe*, June 16-20, 2016, Boston, MA

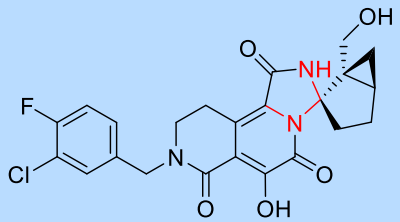
(*N*,*N*)-Aminals: HIV-1 Integrase Strand Transfer Inhibitors



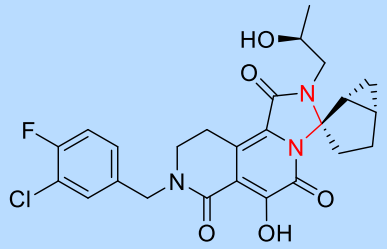
MK-0536
WT IC_{50} = 9 nM
6-fold shift in serum
mutant virus IC_{50}/WT IC_{50} = 1- 3



PSA = 88 Å^2
WT IC_{50} = 2.5 nM
240-fold shift in serum
mutant virus IC_{50}/WT IC_{50} = 1- 6
F = 29% (rats); 27% (dogs)



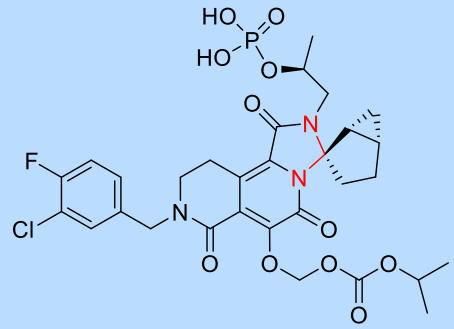
PSA = 98 Å^2
WT IC_{50} = 3 nM
11-fold shift in serum
mutant virus IC_{50}/WT IC_{50} = 1
F = 29% (rats); 27% (dogs)



PSA = 98 Å^2
WT IC_{50} = 2 nM
33-fold shift in serum
mutant virus IC_{50}/WT IC_{50} = 1-1.5
F = 42%, $t_{1/2}$ = 5.9 h in dogs
Solubility = 30 μg/mL (FaSSiF)

- 5-Membered aminal provided the optimal balance of potency and PK
- Addition of the CH_2OH moiety to enhance PSA
  - improved serum-shifted potency
- Insufficient oral exposure in dogs
  - due to limited membrane permeability & solubility
- Pursued a dual prodrug strategy
  - carbonate prodrug addressed membrane permeability challenge
  - phosphate prodrug enhanced aqueous solubility
  - combination afforded high-dose plasma exposure

"*despite the presence of an aminal-type functionality, compounds were chemically and configurationally stable upon isolation*"

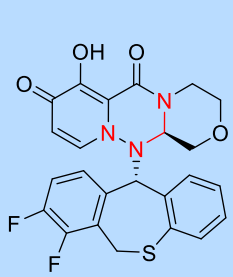


dual prodrug
WT IC_{50} >4.2 μM
Solubility >2 mg/mL (FaSSiF)

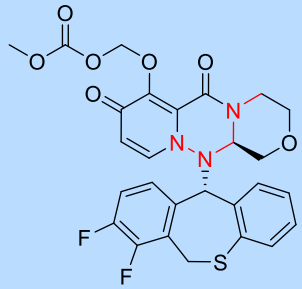
I.T. Raheem *et al*., *J. Med. Chem*., 2015, **58**, 8154-8165

Prominent &/or Recent (*N*,*N*)-Aminals

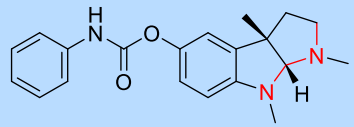
- Baloxavir the 1st new influenza drug in 20 years
  - cap-dependent nuclease (CEN) inhibitor
  - administered as a prodrug
- Phenserine – dual AChE/Aβ inhibitor
  - suspended after Phase 3 trials
- Tomivosertib in clinical trials for cancer in the U.S
  - solid tumors, colorectal cancer
  - diffuse large B-cell lymphoma, prostate cancer
  - non-small cell lung cancer, liver & breast cancer
- ML375 and BTA9881 enantiomeric at the aminal C
  - allosteric modulator of the muscarinic M_5 receptor
  - enantiomer of BTA9881 inactive toward RSV



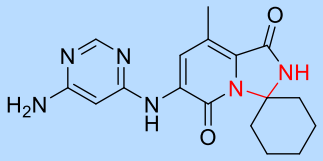
baloxavir
CEN IC_{50} = 2.5 nM
cLog*P* = 2.6
$t_{1/2}$ = 79 h in humans



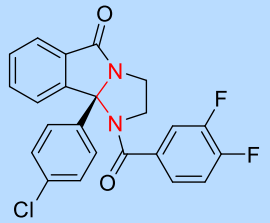
baloxavir marboxil
CEN IC_{50} = 0.53 μM



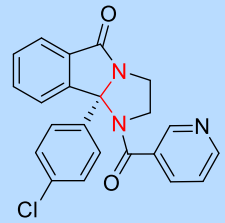
phenserine
dual AChE/Aβ inhibtor
discontinued



tomivosertib (eFT508)
MNK1 IC_{50} = 2.4 nM
MNK2 IC_{50} = 1 nM
cell IC_{50} = 6 nM
F = 25-100% across species



ML375, VU0483253
hM5 IC_{50} = 300 nM
hM1-M4 IC_{50} = > 30 μM
F = 80% in rats
good brain penetration



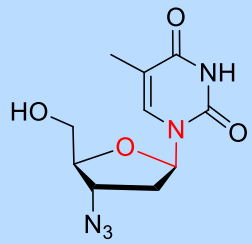
BTA9881
RSV A2 EC_{50} = 48 nM
RSV long EC_{50} = 59 nM
$t_{1/2}$ = 4.5 h
F = 100%

S.H. Reich *et al*., *J. Med. Chem.,* 2018, **61**, 3516-3540; P.R. Gentry *et al*., *J. Med. Chem*., 2013, **56**, 9351-9355
A.G. Draffan *et al*., *Bioorg. Med. Chem. Lett*., 2015, **25**, 976-981; M. Miyagawa *et al., J. Med. Chem.,* 2019, **62**, 8101-8114

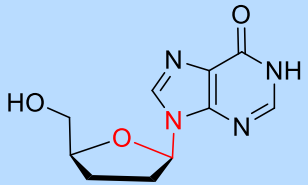
Sulfur-Containing Geminal Diheteroatomics

O,S-Acetals, *O*-CH_2-*S*-Aminal, *N*-CH_2-*S* Derivatives & Thioketals

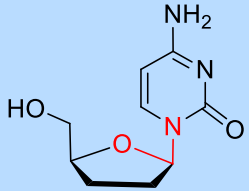
(*O*,*S*)-Hemithio Acetals: 3TC & FTC



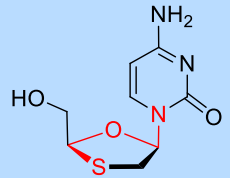
AZT (zidovudine)



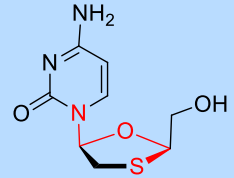
DDI (didanosine)



DDC (zalcitabine)



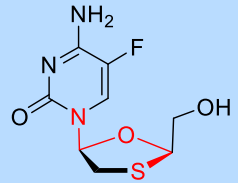
D-(+)-enantiomer of BCH-189
HIV-1 RF IC_{50} = 1.22 μM
HIV-1 LAV EC_{50} = 0.2 μM
cytotoxic



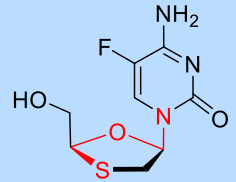
L-(-)-enantiomer of BCH-189
lamivudine (3TC)
HIV-1 RF IC_{50} = 0.87 μM
HIV-1 LAV EC_{50} = 2 nM
F = 82% in man

- Replacement of the DDC ribose C3' with S led to 3TC
  - 3TC was the first biologically active nucleoside with unnatural L-(-)-nucleoside configuration
- (+)-3TC inhibits the constitutive human DNA polymerase, significantly less toxicity than (-)-3TC
  - (-)-FTC is 100-fold more potent than (+)-FTC; both show no cellular toxicity

"Over 90% of HIV infected persons on therapy in the U.S. take a drug containing either 3TC or FTC"



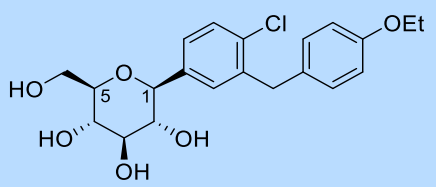
L-(-)-enantiomer
emtricitabine (FTC)
HIV-1 LAV EC_{50} = 8 nM
F = 60-90% in man



D-(+)-enantiomer
HIV-1 LAV EC_{50} = 0.84 μM

D.C. Liotta & G.R. Painter, *Acc. Chem. Res*., 2016, **49**, 2091-2098; G. Dionne, *McGill J. Med.,* 1999, **5**, 60-65; C.K. Chu *et al., FEMS Micobiol. Lett*., 2001, **202**, 9-15

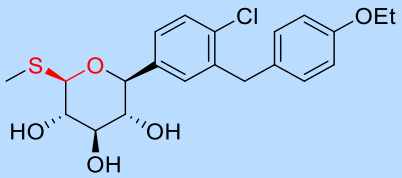
(*O*,*S*)-Acetals: SGLT2 Dual Inhibitors; O-GlcNAcase Inhibitor



dapagliflozin

hSGLT2 IC_{50} = 2.4 nM

hSGLT1 IC_{50} = 392 nM

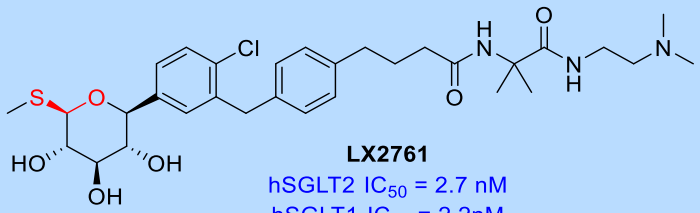


sotagliflozin

hSGLT2 IC_{50} = 1.5 nM

hSGLT1 IC_{50} = 35 nM

$t_{1/2}$ = 7 h; F = 98% in mice



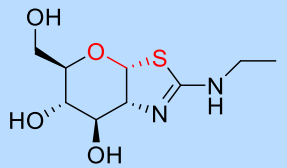
LX2761

hSGLT2 IC_{50} = 2.7 nM

hSGLT1 IC_{50} = 2.2nM

F = < 2% in mice

- Thiomethyl xyloside core imparts SGLT1 potency
  - confers dual SGLT1 & SGLT2 inhibition
  - chemically & metabolically stable
- Sotagliflozin developed to treat type I and II diabetes
  - approved in Europe April, 2019
  - NDA filed December, 2021 following CRL in March 2019
- LX2761: appendage restricts compound to the intestinal lumen
  - locally acting SGLT1 inhibitor
  - currently in Phase 1 for diabetes



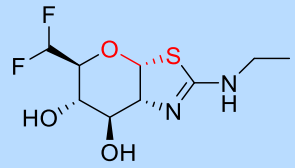
thiamet-G

hOGA K_i = 0.41 nM

rOGA cell EC_{50} = 13.5 nM

P_{app} = <1.0 x 10-6 cm/s

TPSA = 105 Å^2



MK-8719

hOGA K_i = 7.9 nM

rOGA cell EC_{50} = 52.7 nM

P_{app} = 6.4 x 10^{-6} cm/s

TPSA = 80 Å^2

B/P >21 (3 mpk, PO, 24 h, rats)

F = 80% (rat); 90% (dog); 9% (monkey)

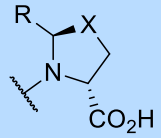
- MK-8719 is a potent O-GlcNAcase inhibitor
  - advanced into Phase 1 clinical trials
  - explored as a therapy to treat neurodegenerative diseases
- Thiamet-G the prototype
  - poor membrane permeability, low CNS penetration
  - high TPSA of 105 Å^2
  - replaced CH_2OH with CHF_2
- Replaced CH_2OH with CHF_2: TPSA = 80 Å^2
  - good CNS penetration
  - high metabolic stability

CRL: complete response letter

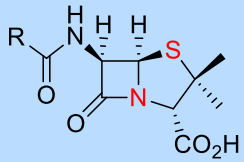
N.C. Goodwin *et al*., *J. Med. Chem*., 2017, **60**, 710-720; H.G. Selnick *et al*., *J. Med. Chem*., 2019, **62**, 10062-10097

(*N*,*S*)-Acetals: Prevalent in Nature – β-Lactam Antibiotics

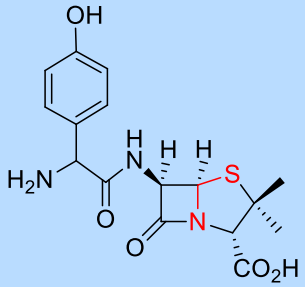
pseudo-proline derivatives
thia-pseudo proline



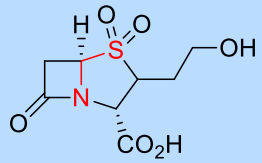
pseudoprolines
X = O, S, NR



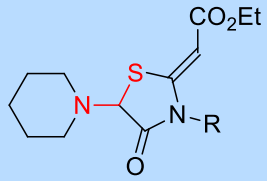
penicillins



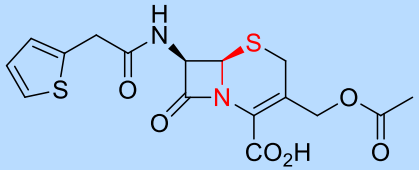
amoxicillin



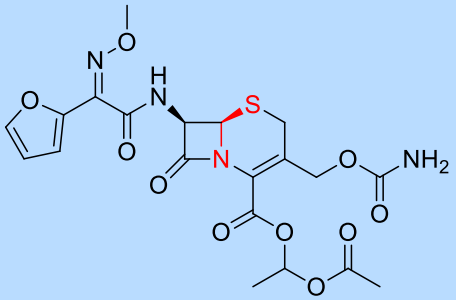
sulbactam
β-lactamase inhibitor



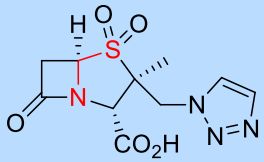
R = Me, **etozolin**
R = Et, **piprozolin**
loop diuretics in Europe



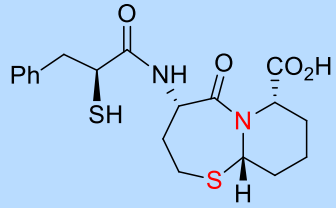
cefalotin



cefuroxime axetil



tazobactam
β-lactamase inhibitor



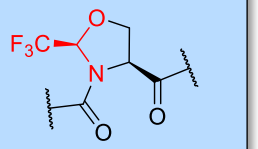
omapatrilat
dual NEP/ACE inhibitor
(discontinued due to side effects)

- N-C-S moiety embedded in penicillin & cephalosporin anti-bacterial agents
  - strained & reactive systems
  - motif exploited in omapatrilat

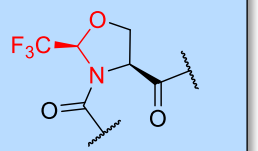
Y.-J. Wu & N.A. Meanwell, *J. Med. Chem.*, 2021, **64**, 19786-9874; J.A. Robl *et al., J. Med. Chem.*, 1997, **40**, 1570-1577

Pseudo-Prolines: (*N*,*O*)- Aminals and (*N*,*S*)-Thioaminals

- Pseudo-prolines: 2 families of proline analogues that incorporate heteroatoms
  - affect ring puckering & amide topology
- Are embedded in penicillins & clavulanic acid
  - well-explored, small molecule context
- Exploited in ACE inhibitor design
  - thia-pseudo-Pro & thia-iso-pseudo-Pro potency similar to captopril
  - rentiapril advanced into Phase 2 clinical studies in Japan but terminated 1994
- Pidotimid is an immune stimulant approved in Europe for respiratory infections
  - F = 42-44%; also given IV; excreted unchanged by the kidneys
  - MK-8325 an advanced HCV NS5A inhibitor
- CF_3-pseudoprolines completely stable under acidic conditions
  - 5% TFA in $CDCl_3$ for days
  - CF_3 improves acid stability due to electron withdrawing properties
- CF_3 increases preference for *cis* amide conformation due to steric hindrance
  - CF_3 locally modulates peptide conformation & promotes *trans* to *cis* isomerization
- CF_3-pseudoprolines are useful tools in studying peptide bioactive conformations
  - synthetic accessibility facilitates structural manipulation & optimization

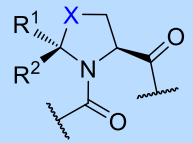


trans amide bond



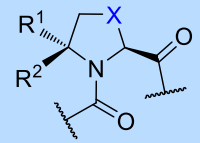
cis amide bond

pseudo-prolines

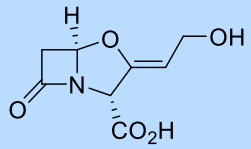


X = O, S, Si

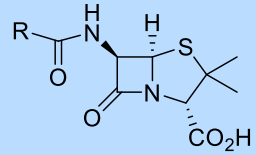
iso-pseudo-prolines



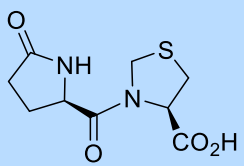
X = O, S, Si



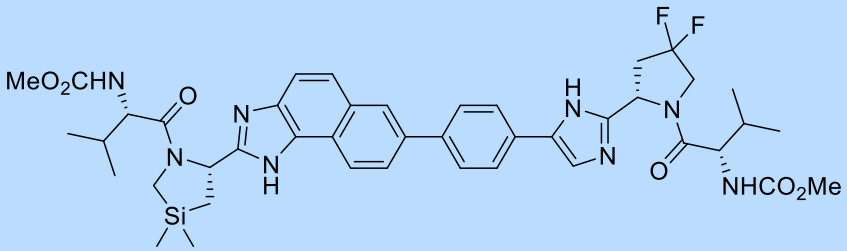
clavulanic acid
β-lactamase inhibitor



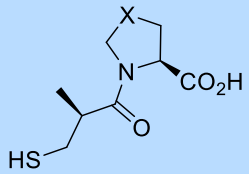
penicillin core
antibiotic



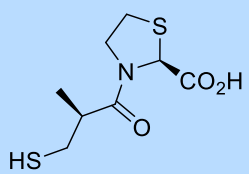
pidotimod



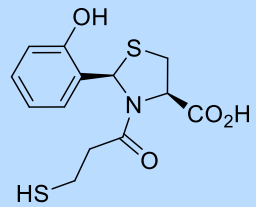
MK-8325



captopril: X = CH_2
ACE pIC_{50} = 6.68
YS-980: X = S
ACE pIC_{50} = 6.43



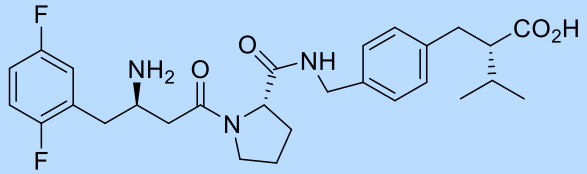
ACE pIC_{50} = 6.08



rentiapril
ACE pIC_{50} = 7.55

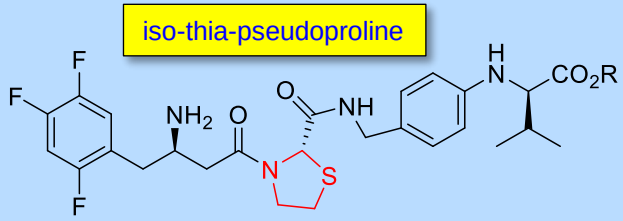
G. Chaume *et al., J. Org. Chem.,* 2010, **75**, 4135-4145; 2013, **78**, 10144-10153; R.K Khan, N.A. Meanwell, H. Hager, *Bioorg. Med. Chem. Lett.,* 2022, **75**, 128983

(*N*,*S*)-Acetals: DPP-4, TGR5; PDE-4, FFA2; HIV-1 Protease

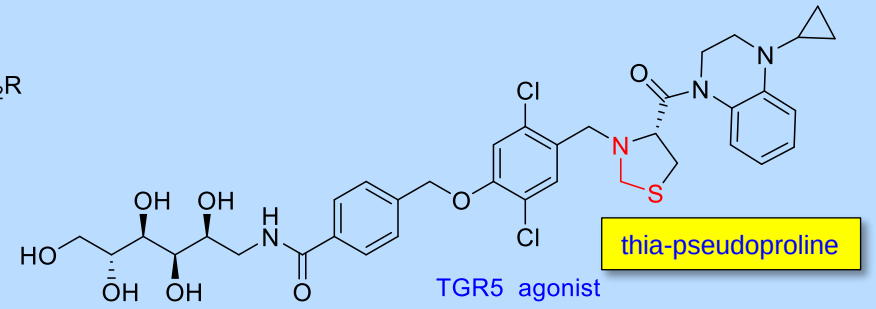


DPP-4 IC_{50} = 0.48 nM
poor oral bioavailability

iso-thia-pseudoproline



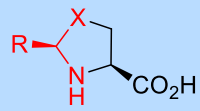
R = H, DPP-4 IC_{50} = 1 nM
chemically and metabolically stable
R = Et, DPP-4 IC_{50} = 17 nM
90% inhibition @ 10 mpk PO (rats)
80% inhibition @ 3 mpk PO (dogs)



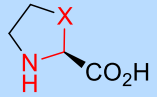
thia-pseudoproline

TGR5 agonist
hTGR5 EC_{50} = 143 nM
mTGR5 EC_{50} = 1.2 nM
minimal systemic exposure

- DPP-4 inhibitor
  - thia-pseudo proline
  - chemical stability favored by C=O



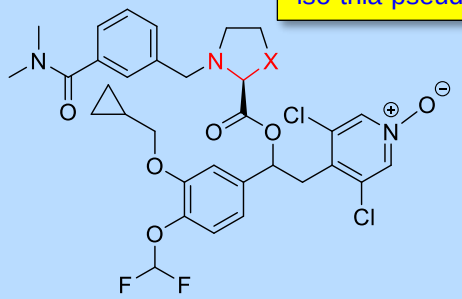
X = O, S, NR
pseudo-prolines



X = O, S, NR
iso-pseudo-prolines

- PDE4 inhibitors
  - inhaled agents for COPD
- Proline derivative
  - low permeability; high protein binding
  - high lung/plasma ratio
- Thiazolidine more active *in vivo*
  - higher lung/plasma ratio
- FFA2: lengthy synthesis
  - thiazolidine core readily made in 3 steps
- Thiazolidine increased potency by 2-fold
- TUG-1375: chemically stable
  - high metabolic & hepatocyte stability
  - high solubility; favorable PK
- GRL-035: potent HIV-1 protease inhibitor

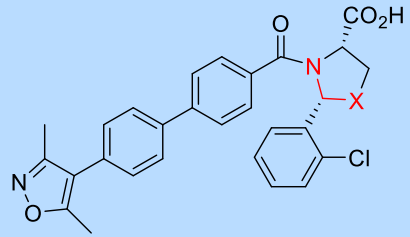
iso-thia-pseudoproline



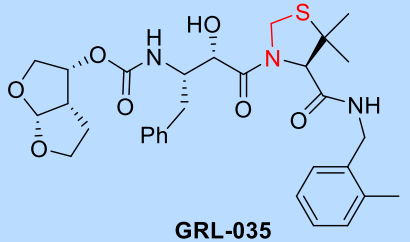
X = CH_2
PDE4 IC_{50} = 0.053 nM
PBMCs IC_{50} = 0.038 nM
in vivo ED_{50} = 0.10 μmol/kg
lung/plasma = 2261

X = S
PDE4 IC_{50} = 0.053 nM
PBMCs IC_{50} = 0.019 nM
in vivo ED_{50} = 0.04 μmol/kg
lung/plasma = 5152

thia-pseudoproline



X = CH_2
FFA2 Agonist, pK_i = 6.4
cAMP pEC_{50} = 6.8
clog*P* = 3.6

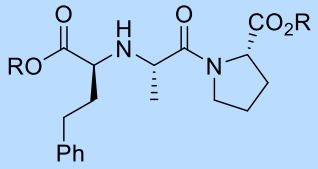


X = S: **TUG-1375**
FFA2 agonist, pK_i = 6.7
cAMP pEC_{50} = 7.1
Log *D* = 0.94 (cLog *P* = 3.6)
Solubility = 182 μM
$t_{1/2}$ = 82 min
F = 32% (mice)

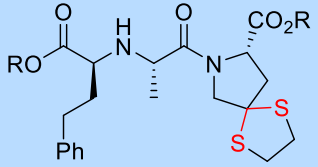
GRL-035
HIV-1 protease inhibitor
IC_{50} = 9 nM

S.D. Edmondson *et al*., *BMCL*, 2004, **14**, 5151-5155; W.S. Park *et al*., *BMCL,* 2011, **21**, 1366-1370; A.H. Hansen *et al., J. Med. Chem*., 2018, **61**, 9534-9550
A.K. Ghosh & D.A. Anderson, *Future Med. Chem*., 2011, **3**, 1181-1197; L. Carzaniga *et al*., *J. Med. Chem*., 2017, **60**, 10026-10046; T. Chen *et al., J. Med. Chem*., 2018, **61**, 7589-7613

Thioketals

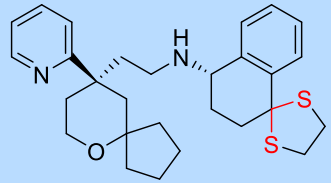


enalaprilat: R = H
enalapril: R = Et (prodrug)
launched in 1985
$t_{1/2}$ = 11 h; F = 60%



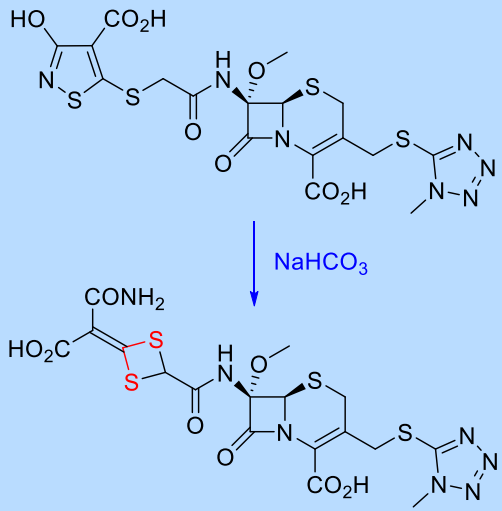
spiraprilat: R = H
spirapril: R = Et (prodrug)
launched in 1995
$t_{1/2}$ = 40 h; F = 50%

ACE inhibitors



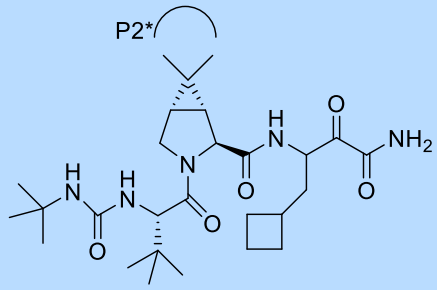
SHR9352
μ-opioid receptor (MOR) agonist
hMOR EC_{50} = 0.77 nM
β-arrestin E_{max} = 19%
rMOR EC_{50} = 0.02 nM
mMOR EC_{50} = 0.19 nM
active @ 0.01 mpk IV

opioid agonist

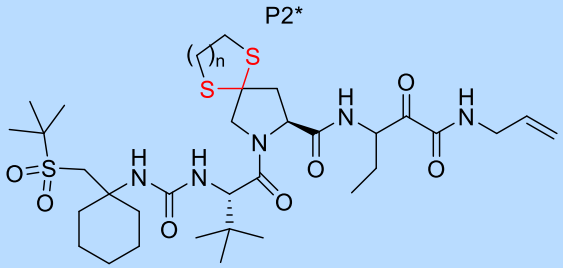


cefotetan

antibiotic



boceprevir
HCV NS3 inhibitor
K_i = 14 nM; EC_{90} = 350 nM
rat AUC = 3.08 μM.h (10 mpk)



2nd generation HCV NS3 inhibitors
n = 2: K_i = 7 nM; EC_{90} = 30 nM
rat AUC = 2.56 μM.h (10 mpk)
n = 1: K_i = 11 nM; EC_{90} = 70 nM
rat AUC = 0.57 μM.h (10 mpk)

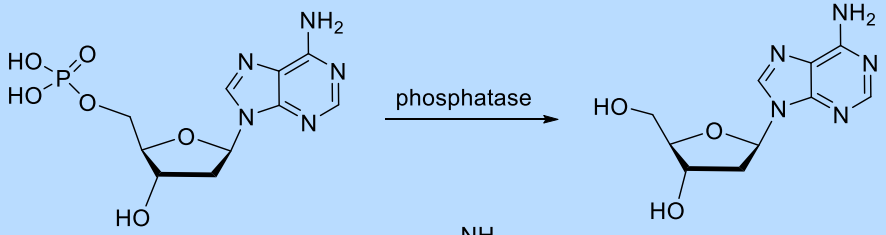
antiviral agents – HCV protease inhibitors

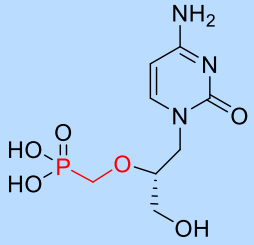
- Spiraprilat/spirapril: ACE inhibitor
  - dithiane homologue of enalaprilat/enalapril
- Designed to be eliminated by the kidney & the liver
  - enalaprilat is cleared through the kidneys
  - longer $t_{1/2}$ in humans

- Cefotetan is an injectable antibiotic: semi-synthetic molecule
  - 1,3-dithietane moiety originated in a rearrangement
  - compound retained potent gram –ve inhibition
  - $NaHCO_3$-mediated isomerization; NaOH or NaOMe reverses
  - used as the final step in the commercial synthesis
- Boceprevir the 1st HCV NS3 PI to be FDA-approved (2011)
  - mechanism-based inhibitor: activated C=O
- Search for a 2nd generation inhibitor embraced thioketal P2* moieties
  - orally bioavailable in rats

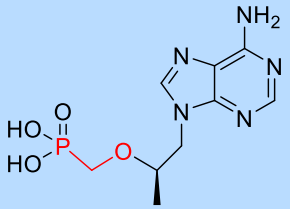
E.M. Smith *et al*., *J. Med. Chem*., 1989, **32**, 1600-1606; X. Li *et al*., *ACS Omega,* 2017, **2**, 9261-9267; M. Iwanami *et al*., *Chem. Pharm. Bull. Jpn*., 1980, **28**, 2629-2636
M. Fujimoto *et al., Org. Proc. Res. Dev*., 2004, **8**, 915-919; S. Venkatraman *et al., J. Med. Chem*., 2006, **49**, 6074-6086; L.G. Nair *et al., Bioorg. Med. Chem. Lett*., 2010, **20**, 1689-1692

O-CH_2-P in Acyclic Nucleoside Phosphonates

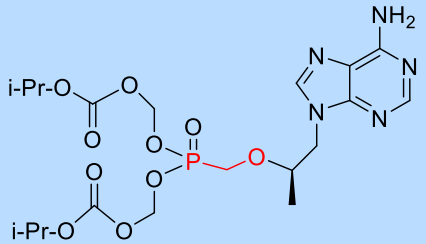




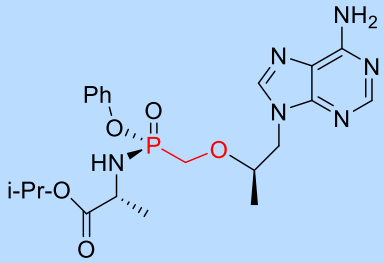
cidofovir
stable to phosphatases
cytomegalovirus retinitis



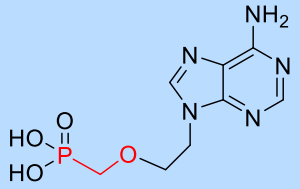
tenofovir
HIV/HBV



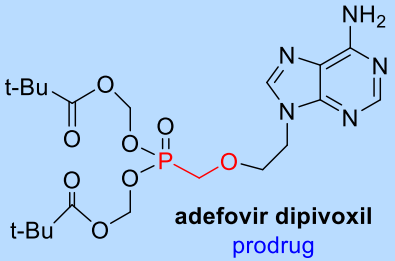
tenofovir disoproxil (TDF)
prodrug, F = 25%



tenofovir alafenamide (TAF)
prodrug, F = 17%



adefovir
HBV

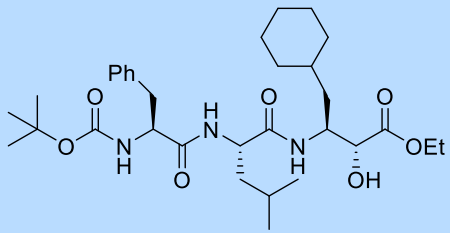


adefovir dipivoxil
prodrug

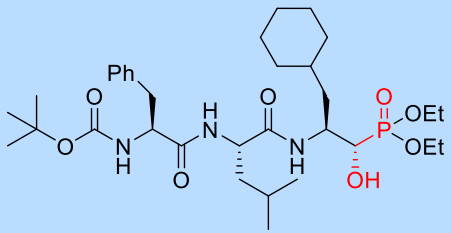
- Tenofovir & cidofovir undergo sequential phosphorylations to give triphosphate mimic
  - triphosphate is active compound that inhibits polymerase via chain termination
- Many nucleoside analogs not phosphorylated effectively *in vivo*
  - 1st phosphorylation step slow & rate-limiting
- Incorporation of a phosphate may help, but O-P bond susceptible to phosphatase cleavage
- Isosteric & isoelectronic phosphonate improve chemical & metabolic stability
- O-CH_2-P resistant to phosphodiesterase & phosphatase hydrolysis
  - more stable than O-P bond
  - chemically and enzymatically stable

E. De Clercq & A. Holý, *Nature Rev. Drug Discov.,* 2005, **4**, 928-940; F. Pertusati *et al*., *Antiviral Chem. Chemother.,* 2012, **22**, 181-203

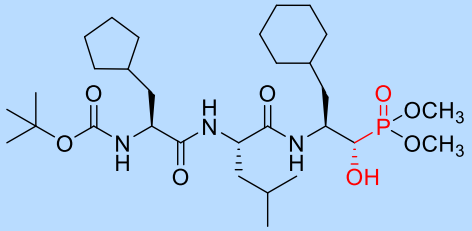
α-Hydroxy Phosphonates: Renin Inhibitors



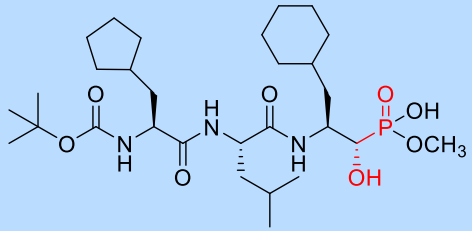
human renin IC_{50} = 5 nM



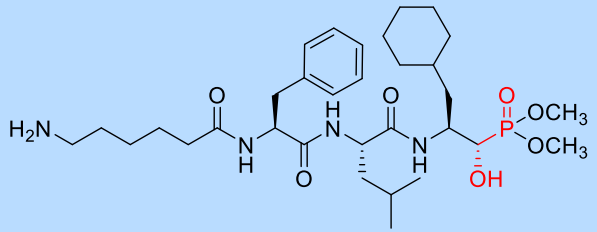
human renin IC_{50} = 29 nM



human renin IC_{50} = 16 nM



human renin IC_{50} = 37 μM



human renin IC_{50} = 31 nM

active *in vivo* (IV, PO)

- α–Hydroxy phosphonates: novel transition state analog inhibitors of human renin
  - mimics of α–hydroxy esters
  - active *in vivo* (IV, PO)
- P-C-OH linkage appears to be chemically & metabolically stable
- Phosphonate ester not acting as a prodrug
  - mono-methyl phosphonate is inactive

D.V. Patel *et al.*, *J. Med. Chem.*, 1995, **38**, 4557-4569

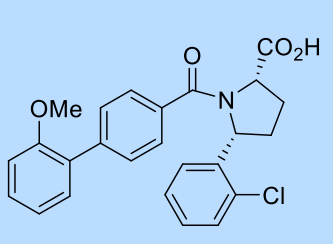
Conclusion

- Geminal diheteroatomic motifs are well represented in marketed drugs
  - prejudice based on perceived instability under acidic conditions
    - degradation in the stomach during oral absorption
  - many examples of orally bioavailable compounds: topirimate
    - stability can easily be tested in simulated gastric fluid
- Chemical stability can be designed rationally
  - typically stabilized by incorporating a proximal EWG
- Acetals, ketals and their sulfur & nitrogen homologues are typically easily prepared
  - a simple condensation reaction
  - can facilitate rapid SAR development
- Acetal/ketal motif can be beneficial in drug design
  - improve potency, solubility, membrane permeability, brain penetration & PK
  - can also overcome hERG, Ca^{2+}channel activity
  - can modulate conformation
- *N,O*- & *N,S*-Aminals
  - HCV NS5A inhibitors; HIV-1 integrase inhibitors
- *O,S*-Ketals
  - HIV-1 inhibiting nucleoside analogues (3TC/FTC)
- *S,S*-ketals
  - ACE inhibitor

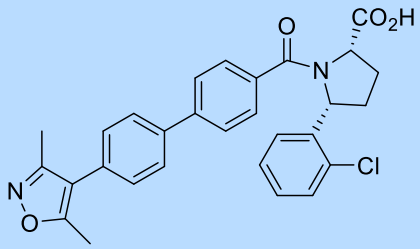
Yong-Jin Wu
Bristol Myers Squibb Research & Early Development
Cambridge, MA

Additional Slides

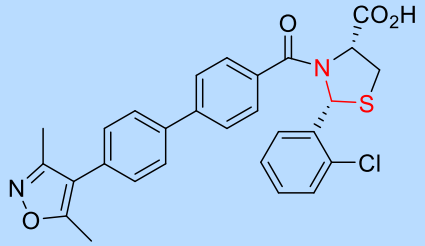
(*N*,*S*)-Acetals: Free Fatty Acid Receptor 2 Agonists



FFA2 Agonist, pK_i = 6.3
cAMP pEC_{50} = 6.3
clog*P* = 5.1



FFA2 Agonist, pK_i = 6.4
cAMP pEC_{50} = 6.8
clog*P* = 3.6

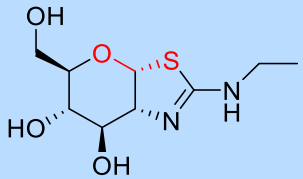


TUG-1375
FFA2 agonist, pK_i = 6.7
cAMP pEC_{50} = 7.1
log*D* = 0.94 (clog*P* = 3.6)
Solubility = 182 μM
$t_{1/2}$ = 82 min
F = 32% (mice)

- SAR around pyrrolidine core limited due to lengthy synthesis
  - thiazolidine core readily made in 3 steps
  - pseudo-proline moiety
- Thiazolidine replacement increased potency by 2-fold
- TUG-1375 has high chemical, metabolic and hepatocyte stability
  - high solubility; favorable PK

A.H. Hansen *et al., J. Med. Chem.*, 2018, **61**, 9534-9550

(*O*,*S*)-Acetals



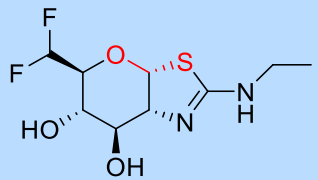
thiamet-G

hOGA K_i = 0.41 nM

rOGA cell EC_{50} = 13.5 nM

P_{app} = <1.0 x 10-6 cm/s

TPSA = 105 Å^2



MK-8719

hOGA K_i = 7.9 nM

rOGA cell EC_{50} = 52.7 nM

P_{app} = 6.4 x 10^{-6} cm/s

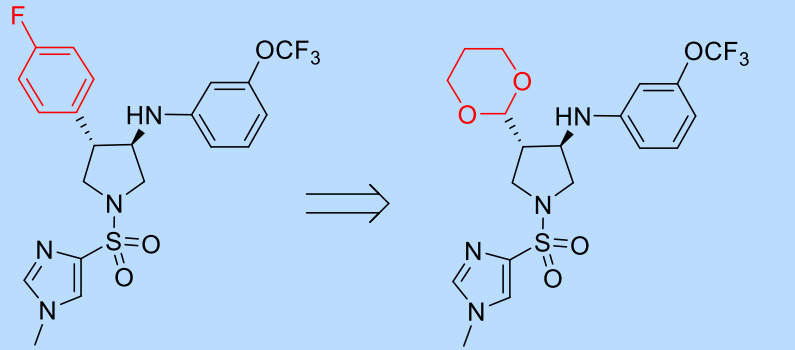
TPSA = 80 Å^2

B/P >21 (3 mpk, PO, 24 h, rats)

F = 80% (rat); 90% (dog); 9% (monkey)

- MK-8719 is a potent O-GlcNAcase inhibitor
  - advanced into Phase 1 clinical trials to treat neurodegenerative diseases
- Thiamet-G the prototype
  - poor membrane permeability, low CNS penetration
  - high TPSA of 105 Å^2
  - replaced CH_2OH with CHF_2
- Replaced CH_2OH with CHF_2
  - TPSA = 80 Å^2
  - good CNS penetration; high metabolic stability

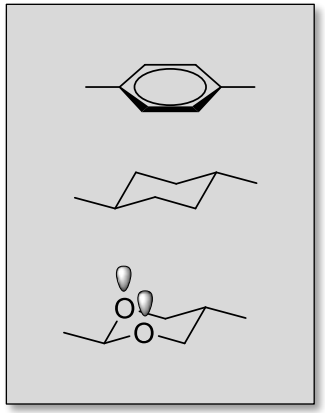
1,3-Dioxane as Phenyl Isostere in GlyT1 & p38 Inhibitors



hGlyT1 K_i = 4 nM
cLog *P* = 4; F_{sp3} = 0.29
$mCl_{int,u}$ = 227 (h)/328 (r) $h^{-1}kg^{-1}$
F = 25% (rat)

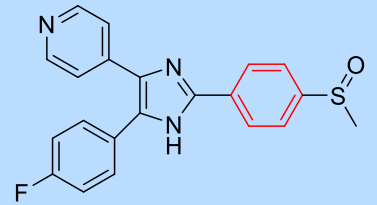
hGlyT1 K_i = 2 nM
cLog *P* = 1.1; F_{sp3} = 0.47
$mCl_{int,u}$ = 6 (h)/8 (r) L $h^{-1}kg^{-1}$
F = 35% (rat)
ED_{50} = 0.9 mpk

- Dioxane remained intact at pH = 1 for 2 days
- Ketal stabilized by adjacent amine
- F-Ph → cyclic acetal led to reduced clearance in HLM & RLM
  - increased fraction of saturated carbons
  - improved oral bioavailability in rats

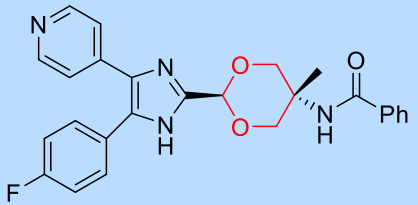


"It is possible to replace a phenyl group with a cyclohexyl group and maintain or improve the potency 60-75% of the time"

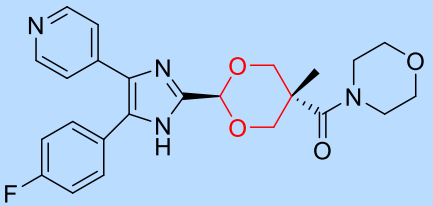
"dioxanes are mimics of cyclohexanes"



SB203580
cLog *P* = 3.0; Fsp^3 = 0.05
p38 MAP kinase IC_{50} = 56 nM
ED_{50} = 10-30 mpk
F = 10-17% in rats
inducer of chromosome damage/CYP1A1



RPR201227A
cLog *P* = 3.2; Fsp^3 = 0.19
p38 MAP kinase IC_{50} = 44 nM
ED_{50} = 10-30 mpk
F = 64% in rats
non-inducer

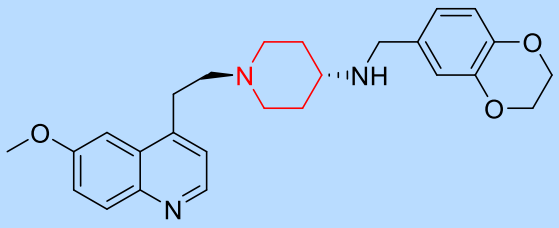


RPR200765A
cLog *P* = 2.3; Fsp^3 = 0.38
p38 MAP kinase IC_{50} = 50 nM
ED_{50} = <10 mpk
F = 50% in rats
non-inducer

- Highly stable in acidic, basic and oxidative environments
- Acetal motif contributed to superior oral efficacy & minimal toxicity

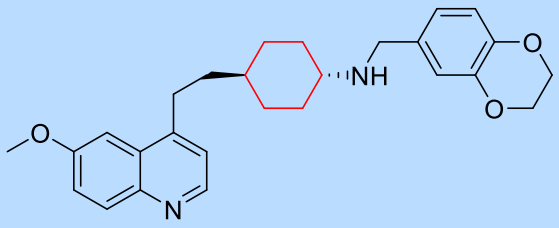
Y. Wang *et al.*, *J. Med. Chem.*, 2018, **61**, 7486-7502; I.M. McClay *et al., Bioorg. Med. Chem.*, 2001, **9**, 537-554
H. Gunaydin & M.D. Bartberger, *ACS Med. Chem. Lett.*, 2016, **7**, 341-344; A.J. Ruger *et al.*, *Eur. J. Org. Chem.*, 2010, 3837-3846

5-Amino-1,3-Dioxane-Based Bacterial Topoisomerase Inhibitors



cpK_a = 8.8/9.1
hERG IC_{50} = 0.81 μM

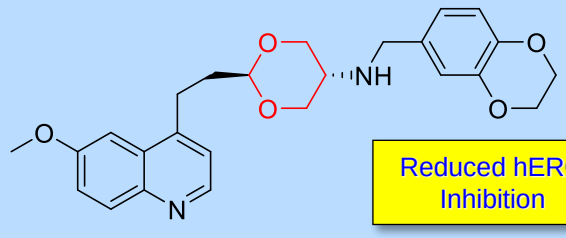
piperidine



cpK_a = 9.5/9.6
hERG IC_{50} = 0.26 μM

cyclohexane

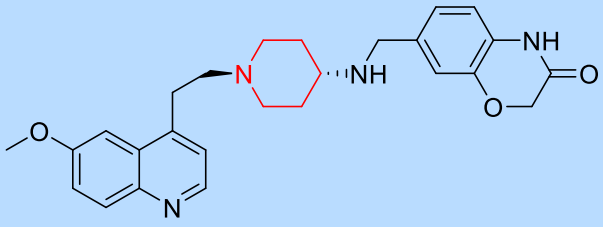
ΔcpK_a = 2.3/1.5



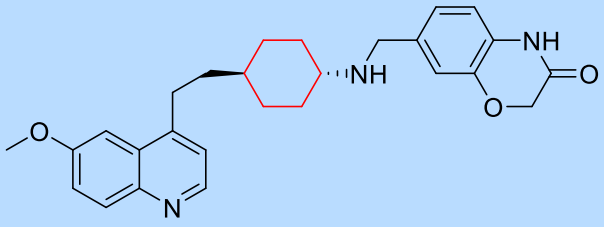
Reduced hERG Inhibition

cpK_a = 7.2/8.1
hERG IC_{50} = 5.1 μM

dioxane

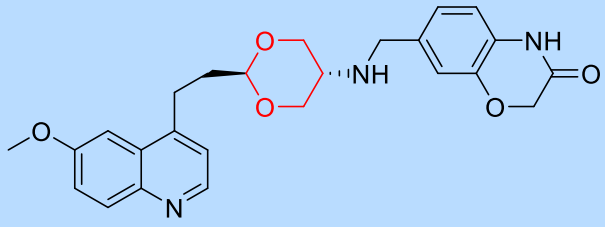


cpK_a = 8.3/9.1
hERG IC_{50} = 1.9 μM



cpK_a = 7.9/8.9
hERG IC_{50} = 0.94 μM

ΔcpK_a = 2.0/1.4



cpK_a = 5.5/7.5
hERG IC_{50} = 9.5 μM

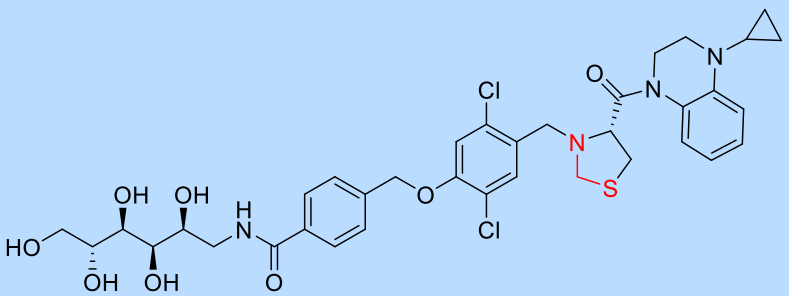
- Acetal linker less basic: calculated pK_a values reduced
  - associated with 2- to 20-fold reduced hERG inhibition
- Dioxane acts as a mimic of cyclohexane in this context

cpK_a data calculated using ACD Labs pK_a & ChemDraw Professional 15.0

hERG inhibition data generated using a high-throughput patch clamp assay

L. Li *et al*., *Bioorg. Med. Chem. Lett*. 2018, **28**, 2477-2480

(*N*,*S*)-Ketals



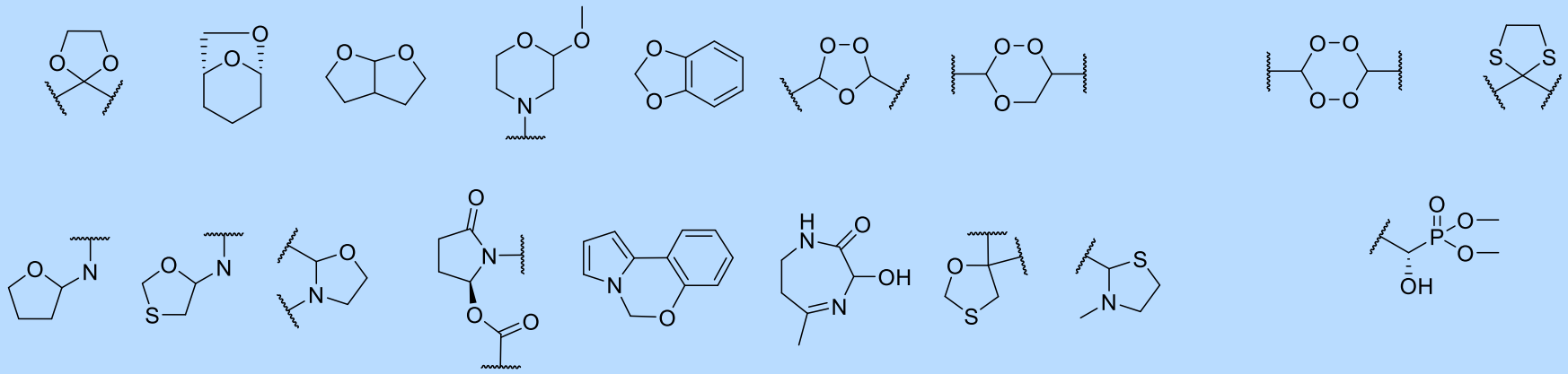
TGR5 agonist
hTGR5 EC_{50} = 143 nM
mTGR5 EC_{50} = 1.2 nM
minimal systemic exposure

T. Chen *et al.*, *J. Med. Chem.*, 2018, **61**, 7589-7613

Geminal Diheteroatomic Motifs

Marketed Drugs

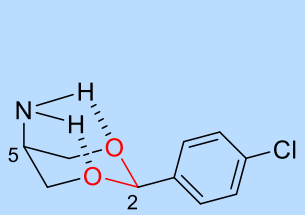
Preclinical Compounds



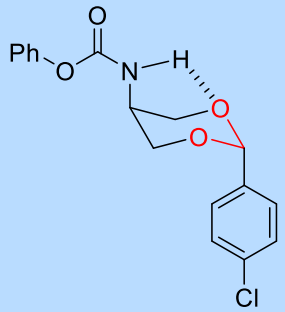
- Geminal diheteroatom motifs are well-represented in marketed drugs
  - prevalent in preclinical compounds
- Wide range of motifs have been explored
  - ketals, acetals, aminals & hemiaminals, thioaminals

Y.-J. Wu & N.A. Meanwell, *J. Med. Chem*., 2021, **64**, 9786-9874

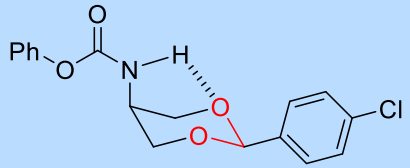
Intramolecular H-Bond & Dioxane Conformation



67% inhibition (*cis* or *trans*) (20 mpk, PO)
41% for aspirin (30 mpk, PO)
(xylene-induced ear edema)



47% inhibition (20 mpk, PO)
(xylene-induced ear edema)

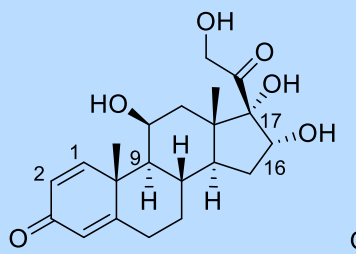


48% inhibition (20 mpk, PO)
(xylene-induced ear edema)

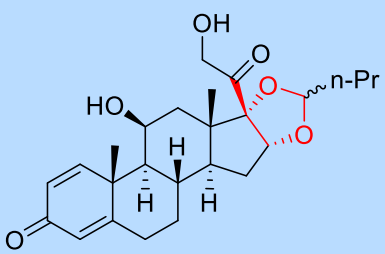
- 5-Amino group adopts axial orientation for both *cis* & *trans* isomers (NMR studies)
  - stabilized by an intramolecular H-bonding interaction
- Some 4-aryl, heteroaryl analogs showed comparable or better anti-inflammatory activity than aspirin
  - activity is due to the intact acetal
  - constituent aldehydes & aminodiols inactive *in vivo*
- Weak PKC inhibitory activity
  - MOA to be determined

L. Bi *et al*., *Bioorg. Med. Chem.,* 2005, **13**, 5640-5646; 2006, **14**, 1339-1347; 2007, **15**, 6273-6290; 2008, **16**, 1764-1774

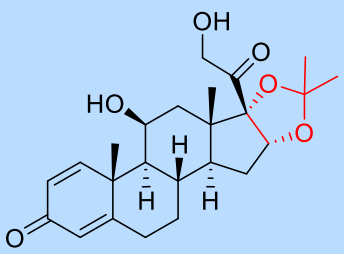
Inhaled Steroid 16,17-Acetals for Asthma



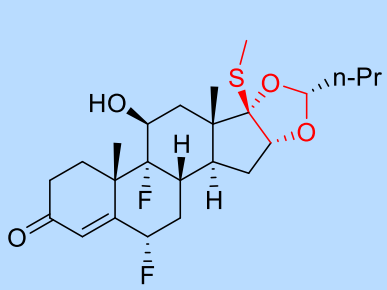
triamcinolone



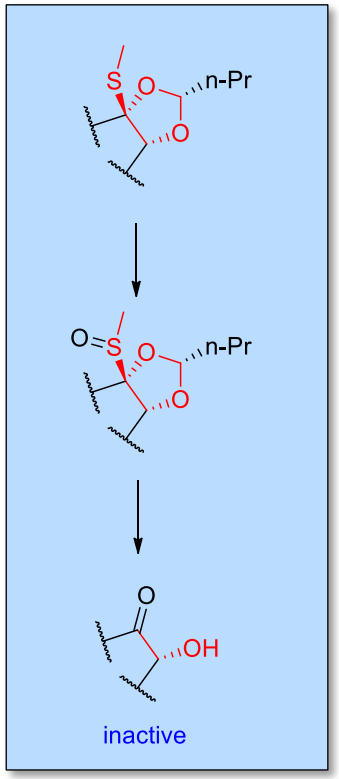
budesonide
GR binding IC_{50} = 2.9 nM
lung edema ED_{50} = 0.39 mpk
thymus involution ED_{50} = 0.96 mpk
topical/systemic ratio = 0.4



triamcinolone acetonide



RPR106541
GR binding IC_{50} = 0.3 nM
lung edema ED_{50} = 0.06 mpk
thymus involution ED_{50} = 1.0mpk
topical/systemic ratio = 0.06

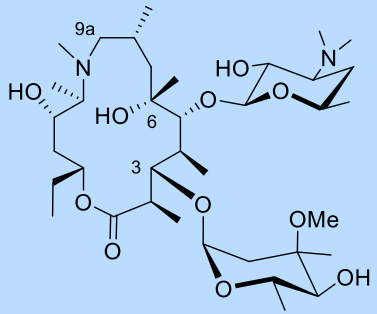


inactive

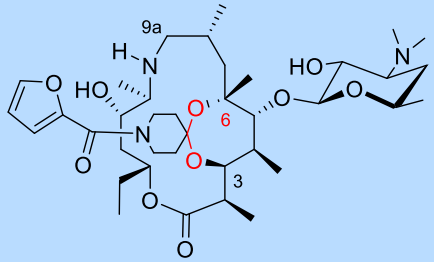
- Triamcinolone & budesonide
  - significant plasma levels
  - systemic side effects (F >10%)
- 16,17-acetal enhances binding to the glucocorticoid receptor
  - projects *n*-Pr into the hydrophobic site
- Topical, airway-selective glucocorticoids are desired for long-term safety
- Enhanced systemic deactivation due to sulfur oxidation followed by hydrolytic decomposition

M.J. Ashton *et al., J. Med. Chem.*, 1996, **39**, 4888-4896

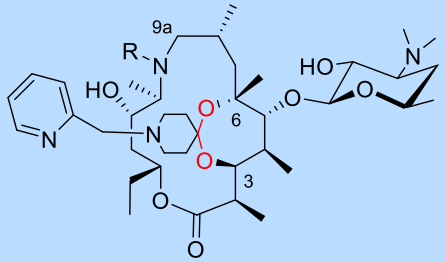
Azalide 9,10-Ketals



azithromycin, MIC
P. multocida: 0.1 μg/mL
E. Coli: 1.56 μg/mL
S. aureus: 0.2 μg/mL



R = H, MIC
P. multocida: 0.05 μg/mL
E. Coli: 0.78 μg/mL
S. aureus: 0.78 μg/mL



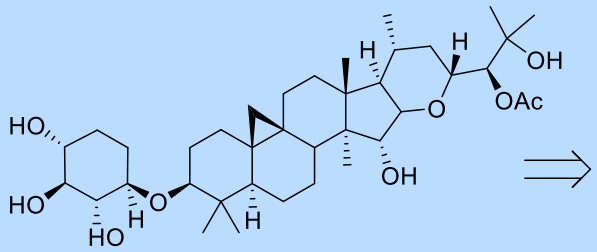
R = H, MIC
P. multocida: 0.03 μg/mL
E. Coli: 0.2 μg/mL
S. aureus: 0.6 μg/mL

R = Me, MIC
P. multocida: 0.03 μg/mL
E. Coli: 0.2 μg/mL
S. aureus: 0.78μg/mL

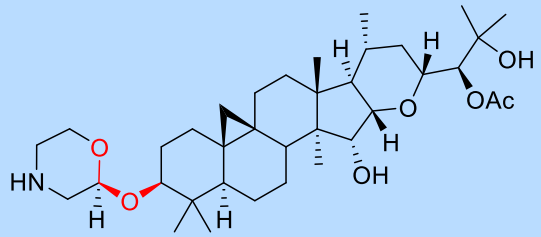
- Azithromycin known for its long tissue $t_{1/2}$
- 3,6-Ketals showed better activity against veterinary pathogens
- Good *in vivo* activity (IP)
- Example of unstabilized ketal with good *in vivo* activity

H. Cheng *et al*., *Bioorg. Med. Chem. Lett*., 2002, **12**, 2431-2434; S.M. Sakya *et al*., *Bioorg. Med. Chem. Lett*., 2003, **13**, 1373-1375

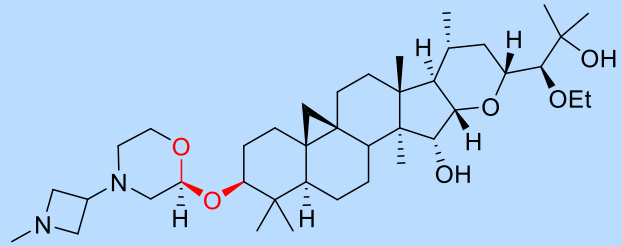
Morpholine-Based Acetals in γ-Secretase Modulators



HBD = 5; tPSA = 155; cLog *P* = 2.6
$A\beta_{42}$ IC_{50} = 60 nM
poor brain penetration



HBD = 3; tPSA = 106; pK_a = 7.7; cLog *P* = 4.1
$A\beta_{42}$ IC_{50} = 70 nM
B/P = 1.7 @ 6 h (30 mpk PO, mice)
F = 37% in mice

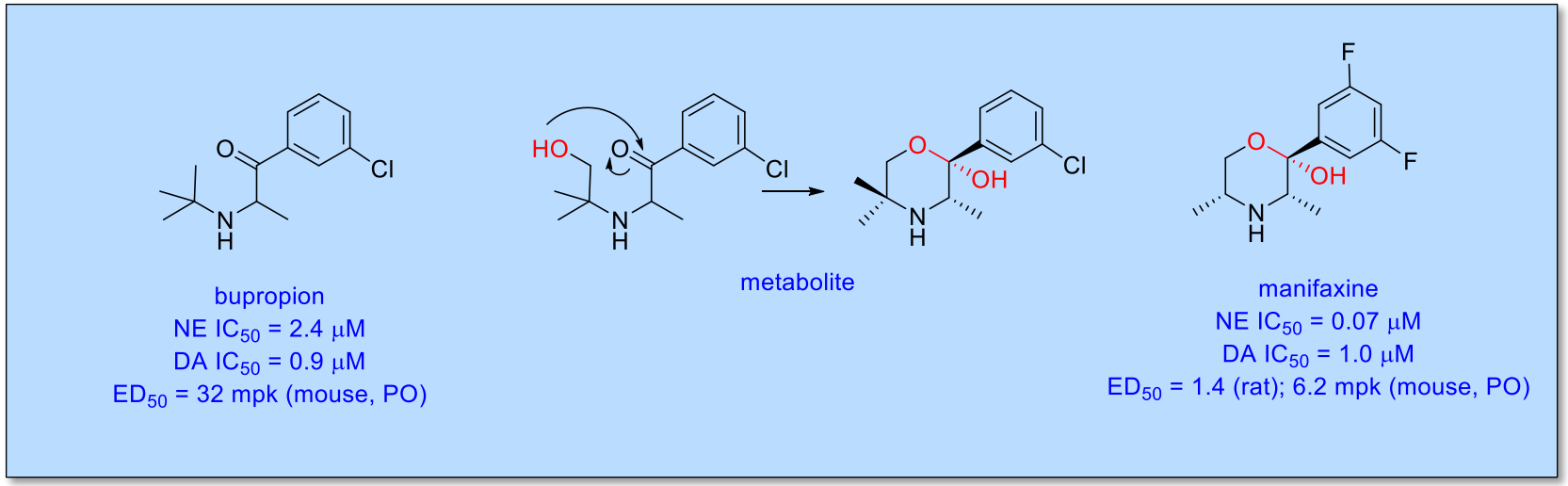


SPI-1865
HBD = 2, tPSA = 84; cLog *P* = 4.9
$A\beta_{42}$ IC_{50} = 100 nM
B/P = 0.55 @ 6 h (30 mpk PO, mice)
F = 75% in mice
lowered $A\beta_{42}$ in vivo

- Optimal CNS drug properties
  - PSA < 90 Å^2; MW <450
- Conversion of native sugar to morpholine lowers the tPSA to 106 Å^2
  - retains γ-secretase inhibitory potency
  - exhibits significantly enhanced brain penetration

J.L. Hubbs *et al., J. Med. Chem.*, 2012, **55**, 9270-9282; N.O. Fuller *et al.*, *ACS Med. Chem. Lett.*, 2012, **3**, 908-913; R. Shen *et al.*, *Org. Proc. Res. Dev.,* 2014, **18**, 676-682

Morpholine Acetals in Norepinephrine Reuptake Inhibitors



bupropion
NE IC_{50} = 2.4 μM
DA IC_{50} = 0.9 μM
ED_{50} = 32 mpk (mouse, PO)

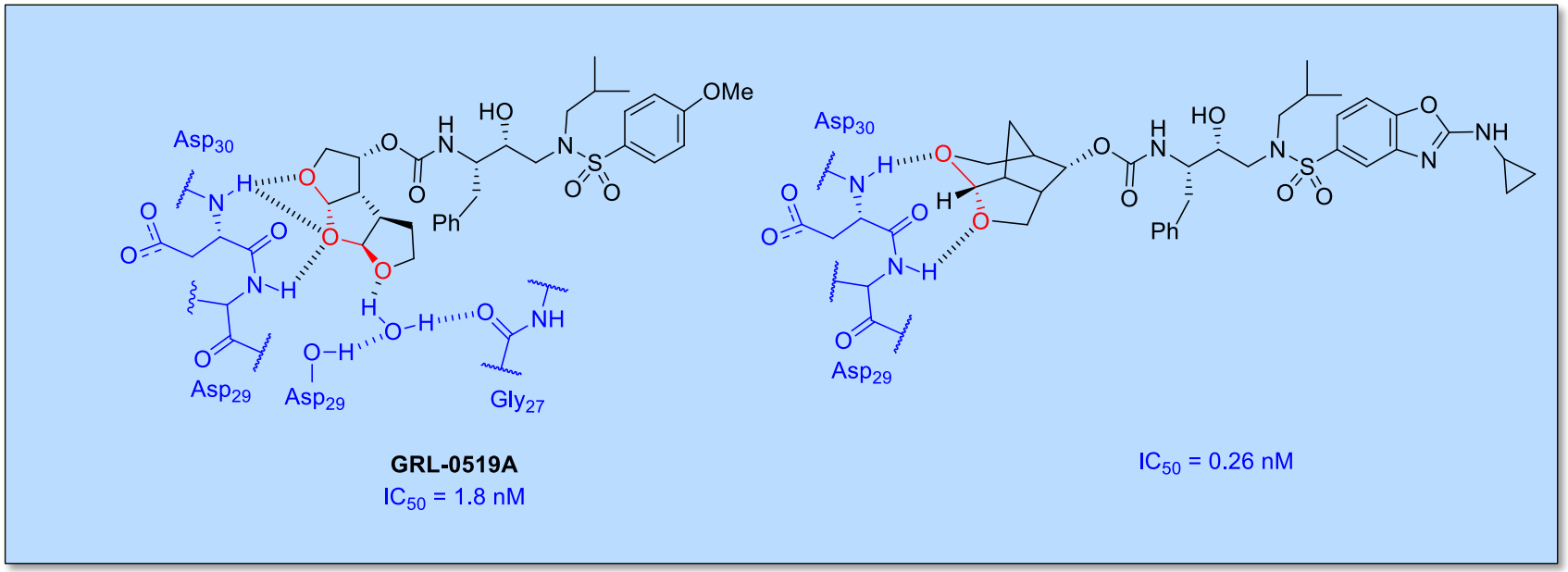
metabolite

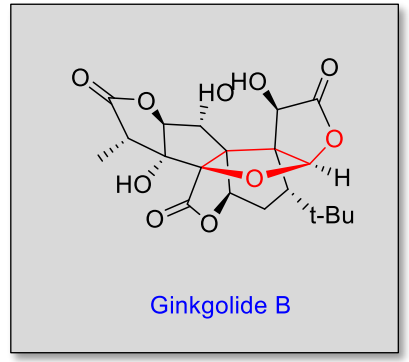
manifaxine
NE IC_{50} = 0.07 μM
DA IC_{50} = 1.0 μM
ED_{50} = 1.4 (rat); 6.2 mpk (mouse, PO)

- Morpholine hemiketal is an active metabolite of bupropion
  - may contribute to *in vivo* activity
- Manifaxine is 30-fold more active than bupropion *in vitro* (NE uptake)
  - 4-fold more active *in vivo*

J.L. Kelley *et al*., *J. Med. Chem*., 1996, **39**, 347-349

Tris-/CrownTHF: P2 Element for HIV-1 Protease Inhibitors

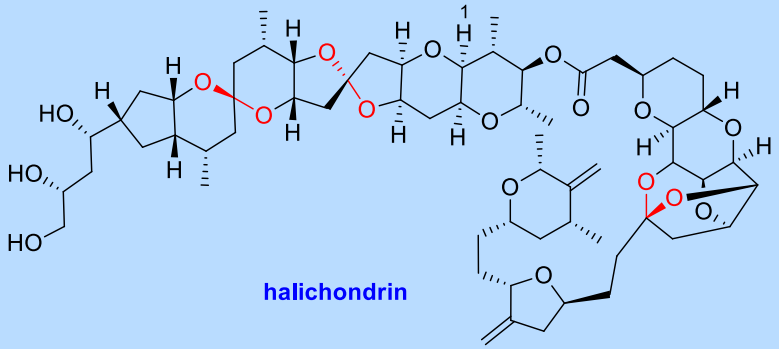




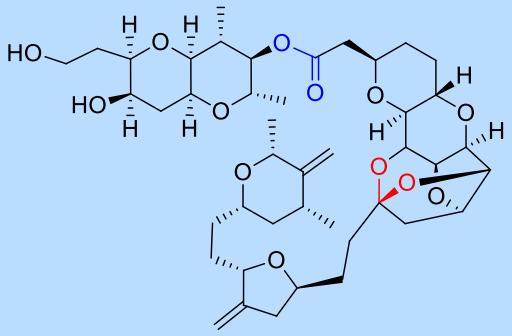
- Additional H-bond and hydrophobic interactions contribute to improved potency

A.K. Ghosh, *J. Med. Chem.*, 2009, **52**, 2163-2175; I.T. Weber *et al., J. Med. Chem.,* 2013, **56**, 1074-1083
A.K. Ghosh *et al.*, *J. Med. Chem.*, 2017, **60**, 4267-4278; *Acc. Chem. Res.*, 2008, **41**, 78-86; *ChemMedChem,* 2006, **1**, 939-950

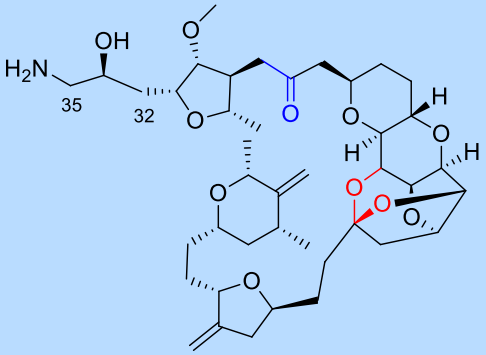
Crown THF in Halichondrin Analogues



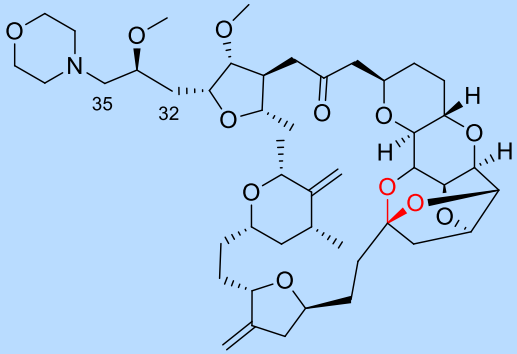
halichondrin



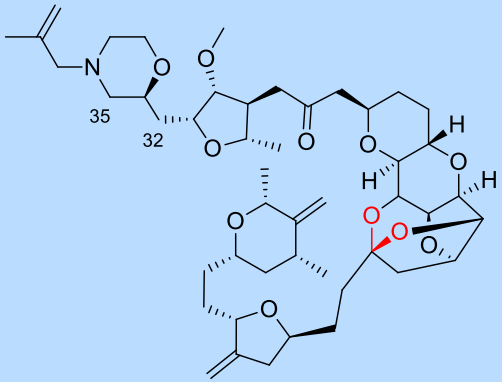
active



eribulin
MES-SA IC_{50} = 1.66 nM
MES-SA/Dx5-Rx1 IC_{50} = 3058 nM
FR = 1842



A
MES-SA IC_{50} = 0.16 nM
MES-SA/Dx5-Rx1 IC_{50} = 1.91 nM
FR = 12



B
MES-SA IC_{50} = 0.25 nM
MES-SA/Dx5-Rx1 IC_{50} = 1.53 nM
FR = 6

- Activity resides in right hand side of halichondrin
- Incorporation of morpholine reduces pK_a and P-gp efflux
  - compound A: orally active; CSF/Plasma = 2.2
  - compound B: active in brain tumor models (IV)

Ghosh, *J. Med. Chem.*,

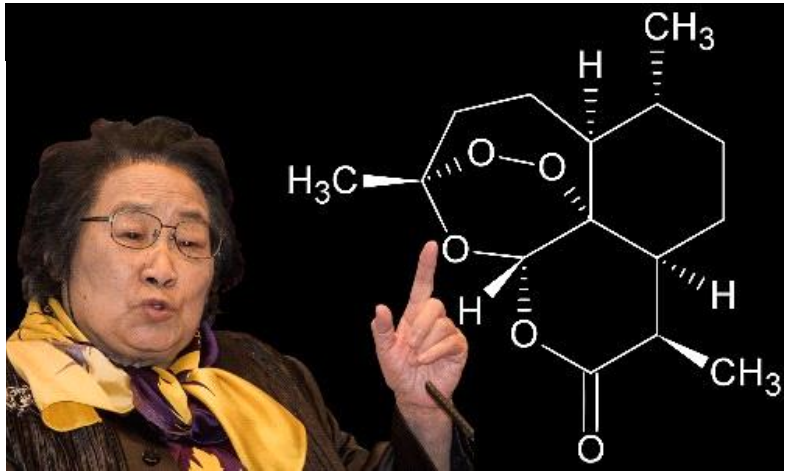
Discovery of Artemisinin

A Handbook of Prescriptions for Emergencies (肘后备急方)

by Ge Hong (283-343) during the Jin Dynasty

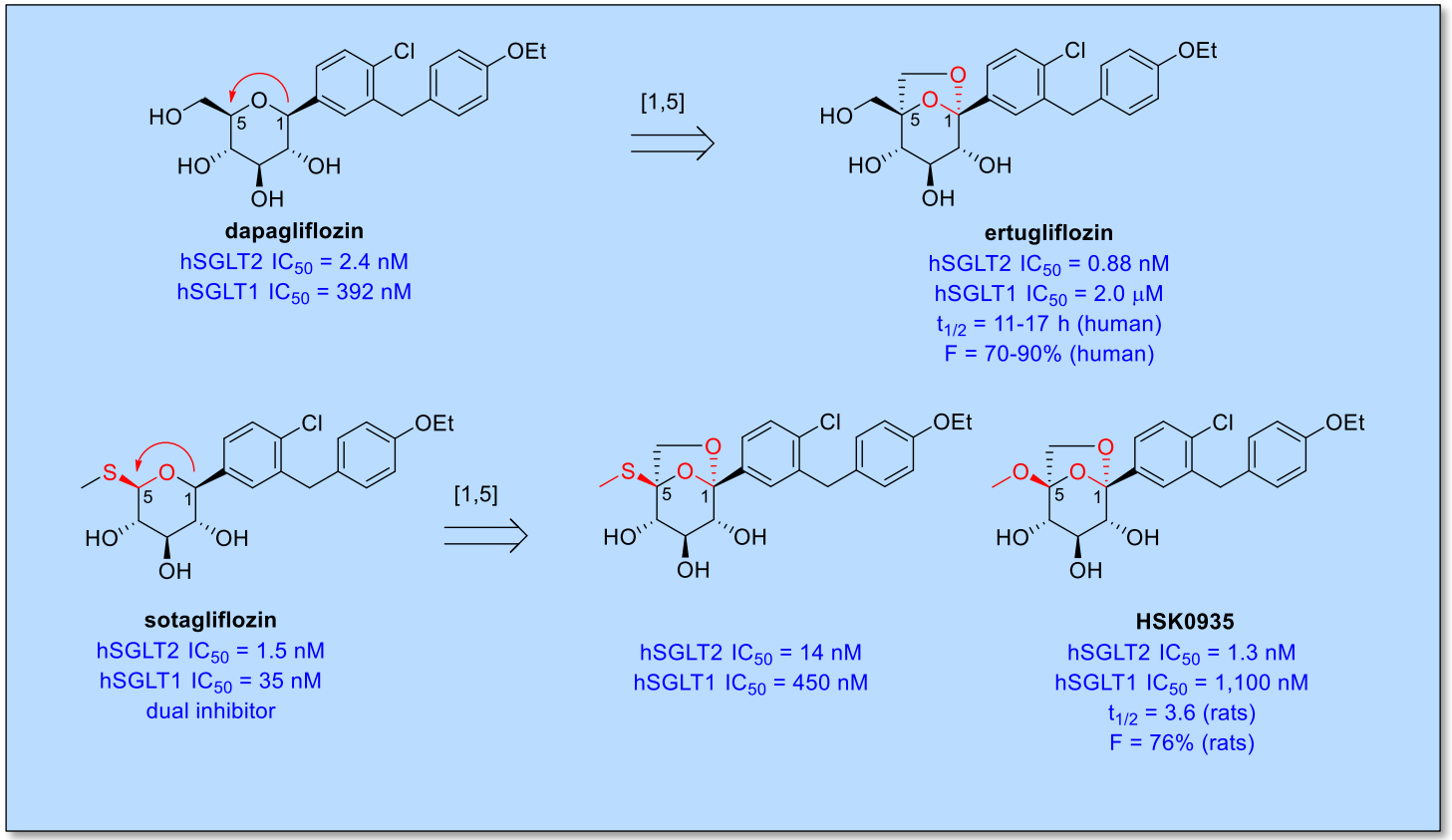
青蒿一握，
以水二升渍，
绞取汁，
尽服之

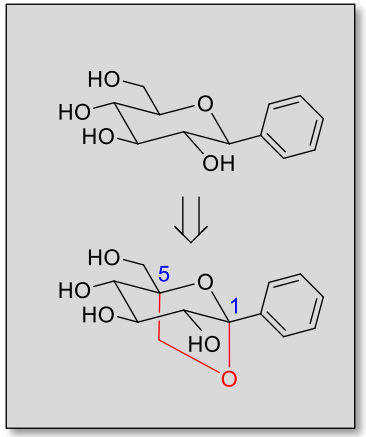
"Take one bunch of qinghao, Soak in two sheng(~0.4 L) of water, wring it out to obtain the juice and ingest it in its entirety"



Collaboration research group for Qinghaosu. A new sesquiterpene lactone - Qinghaosu (in Chinese). *Kexue Tongbao* **1977**, *3*, 142

Spirocyclic Ketals in SGLT2 Inhibitors

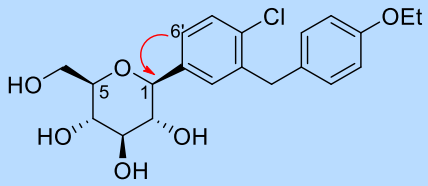




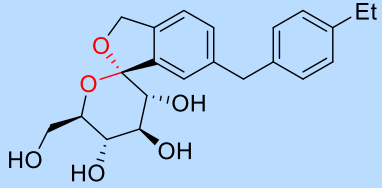
- 1,5-Cyclized ketal positively impacts both potency and selectivity
  - enhances SGLT2 inhibition while weakening SGLT1 inhibition
- Cyclization of sotagliflozin & optimization transformed a dual SGLT1 and 2 inhibitor into a selective SGLT2 inhibitor
  - SCH_3 to OCH_3 enhances SGLT2 inhibition 10x whilst reducing SGLT1 inhibition 2x

V. Mascitti *et al.*, *J. Med. Chem.*, 2011, **54**, 2952-2960; *Med. Chem. Commun.*, 2013, **4**, 101-111; Y. Li *et al.*, *J. Med. Chem.*, 2017, **60**, 4173-4184

Spirocyclic Ketals in SGLT2 Inhibitors

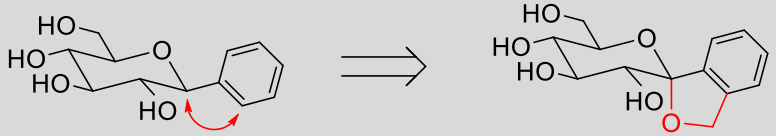


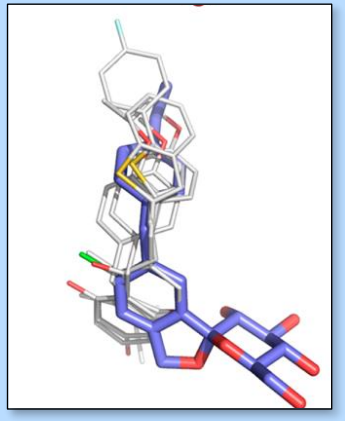
[1, 6']



dapagliflozin
hSGLT2 IC_{50} = 2.4 nM
hSGLT1 IC_{50} = 392 nM

tofogliflozin
hSGLT2 IC_{50} = 2.9 nM
hSGLT1 IC_{50} = 8,400 nM
F = 75% (mouse); 85% (monkey)



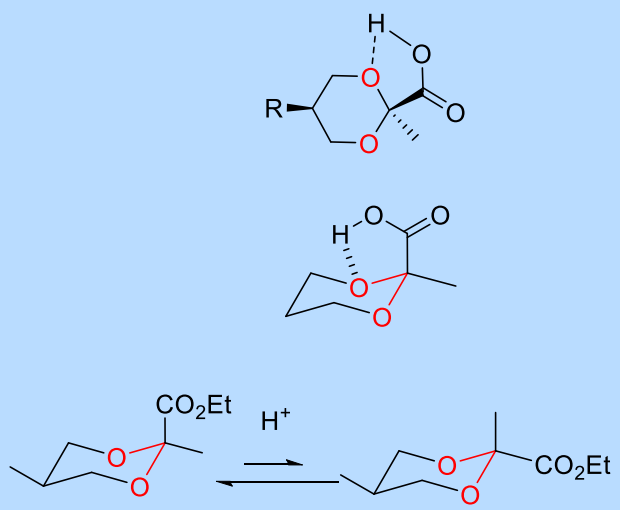


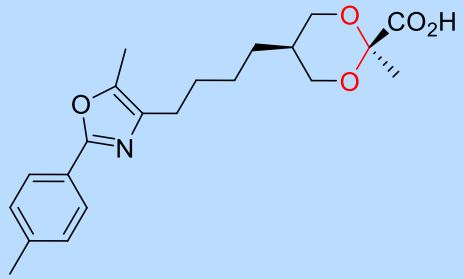
overlap of tofogliflozin & SGLT2 inhibitors

- Lowest energy conformation of SGLT2 inhibitors
  - orthogonal orientation between the glycoside & the phenyl ring
- A 1,6'-cyclized spiroketal moiety enforces a perpendicular orientation
  - cyclization enhanced selectivity for SGLT2 by 20x

Y. Ohtake *et al.*, *J. Med. Chem.*, 2012, **55**, 7828-7840; B. Lv *et al.*, *Bioorg. Med. Chem. Lett.,* 2009, **19**, 6877-6881

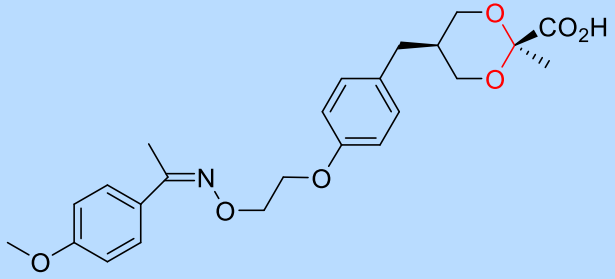
Intramolecular H-Bond & Dioxane Stability





NS-220

hPPARα transactivation:
13-fold induction @ 10 μM
$t_{1/2}$ = 2 h in rats
30 mpk PO QD, 15 days to rats
51% reduction of serum triglycerides
49% reduction of total cholesterol



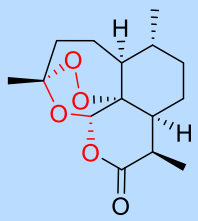
Compound A

hPPARα transactivation:
15-fold induction @ 10 μM
$t_{1/2}$ = 14 h in rats
3 mpk PO QD, 15 days dosing to rats
54% reduction of serum triglycerides
56% reduction of total cholesterol

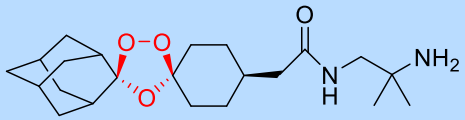
- Acetal carboxylic acid core in peroxisome proliferator-activated receptor α (PPARα) agonists
  - axial ester preferred by anomeric effect
  - acid stabilized by intramolecular H-bond
- Significant hypoglycemic and lipid modulating effects upon oral dosing
- Compound A showed superior oral efficacy due to improved PK

T. Harabe *et al., Tetrahedron,* 2009, **65**, 4044-4052; T. Aoki *et al*., *Bioorg. Med. Chem. Lett*., 2008, **18**, 2128-2132; T. Asaki *et al*., *Bioorg. Med. Chem.,* 2008, **16**, 981-994
P. Zaware *et al*., *Bioorg. Med. Chem. Lett*., 2011, **21**, 628-632; H. Pingale *et al*., *Bioorg. Med. Chem. Lett*., 2008, **18**, 6471-6475

Artemisinin-Inspired Epoxy Ketals: Synthetic Antimalarials

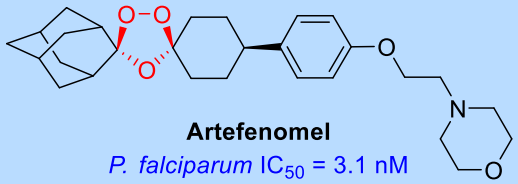


artemisinin



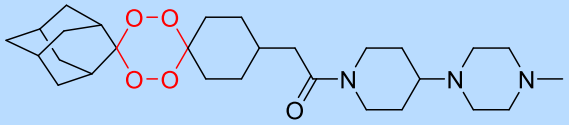
Arterolane

P. falciparum IC_{50} = 1.7 nM
$t_{1/2}$ = 1 h (rats); 3 h (human)
F = 35% (rats)
single dose cures: 0/5 (30 mpk, po)



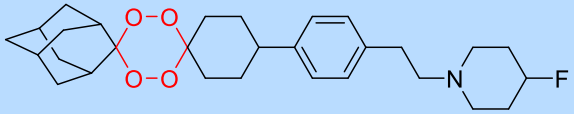
Artefenomel

P. falciparum IC_{50} = 3.1 nM
$t_{1/2}$ = >20 h (rats); 46-60 h (human)
F = 76% (rats)
single dose cures: 5/5 (30 mpk, po)



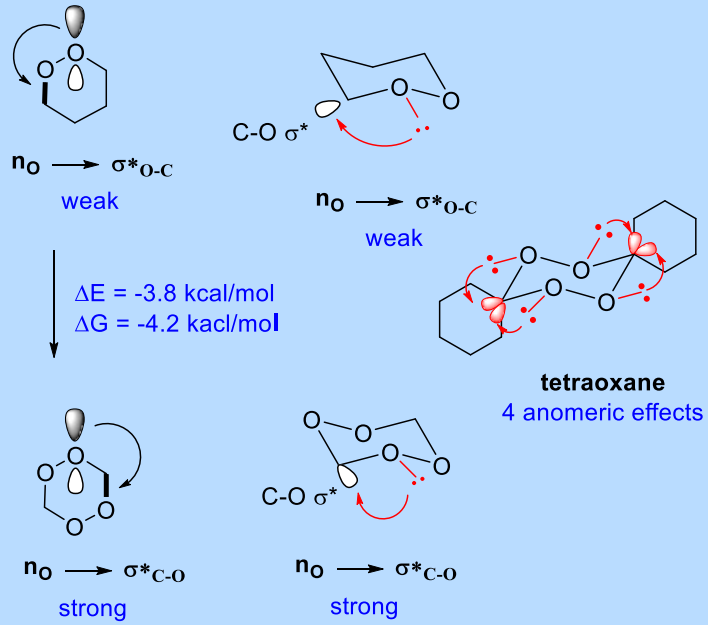
RKA182

P. falciparum (3D7); IC_{50} = 0.8 nM
F = 38% (rat); 42% (mouse)
not compatible with single dose cure



E209

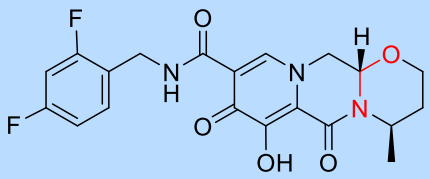
P. falciparum (3D7); IC_{50} = 5.1 nM
F = 62% (rat); 82% (mouse); 40% (dog); 62% (human)
predicted $t_{1/2}$ (human) = 24 - 30 h
compatible with single dose cure



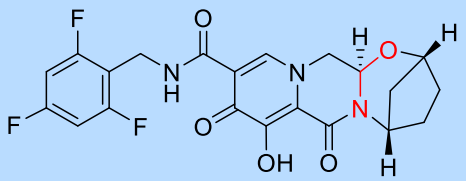
◆ Peroxide acetal motif unusually stable due to a substantial anomeric-like effect

J.L. Vennerstrom *et al*., *J. Med. Chem*., 2010, **53**, 4223-4233; *Proc. Natl. Acad. Sci. U.S.A.*, 2011, **108**, 4400-4405; P.M. O'Neill *et al*., *Nature Commun.,* 2017, 15159
G. dos Passos Gomes *et al*., *Chem. Sci.,* 2015, **6**, 6783-6791; A.O. Terent'ev *et al*., *Org. Biomol. Chem*., 2013, **11**, 2613-2623

(*N*,*O*)-Aminals in HIV-1 Integrase Inhibitors



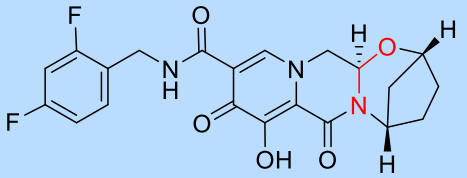
dolutegravir
EC_{50} = 1.7 nM
G140S/Q148R fold shift = 4.8
%free human plasma = 0.7
PXR %Emax @ 15 μM = 51
Solubility = 53 μg/mL (pH 7)
F = 34% (rat); 35% (dog); 25% (cyno)
$t_{1/2}$ = 14 h in humans



bictegravir
EC_{50} = 1.9 nM
G140S/Q148R fold shift = 2.0
%free human plasma = 0.30
PXR %Emax @ 15 μM = 18
Solubility = 119 μg/mL (pH 7)
F = 50% (rat) (52% for dolutegravir) (0.5 mpk, solution)
F = 28% (dog) (17% for dolutegravir) (1 mpk, suspension)
$t_{1/2}$ = 19 h in humans

EC_{50} = 0.5 nM
(1.7 nM for dolutegravir)
2.2-fold change against resistant mutant
(0.4-fold for Dolutegravir)

[2,4]-ring closure

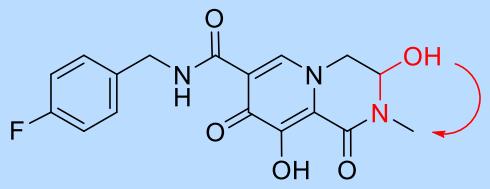


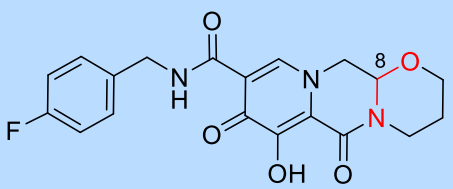
EC_{50} = 2.2 nM
G140S/Q148R fold shift = 3.4
%free human plasma = 0.28
PXR %Emax @ 15 μM = 5

- [3.2.1]-bicyclic system associated with lower PXR activation
- Lower free fraction in human plasma
  - plasma protein binding strongly correlates with mean residence time (MRT) in rats
  - $t_{1/2}$ = 19 h in humans (14 h for dolutegravir)
- Additional F atom on phenyl ring improved aqueous solubility

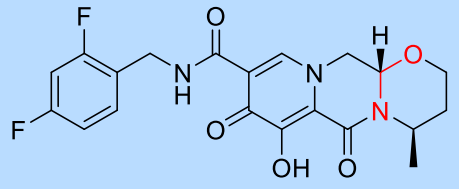
S.E. Lazerwith *et al*., *ASM Microbe*, June 16-20, 2016, Boston, MA; . Kawasuji *et al*., *J. Med. Chem*., 2013, **56**, 1124-1135; B.A. Johns *et al*., *J. Med. Chem.,* 2013, **56**, 5901-5916

(*N*,*O*)-Aminals in HIV-1 Integrase Inhibitors

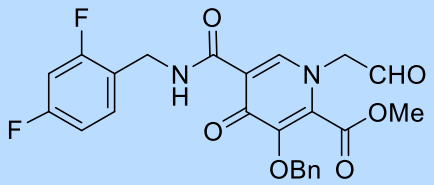


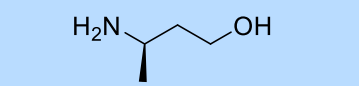


8*S*: IC_{50} = 1.9 nM; PA IC_{50} = 81 nM
F = 79% (rat)
8*S*: IC_{50} = 2.2 nM; PA IC_{50} = 9.4 nM
F = 52% (rat)

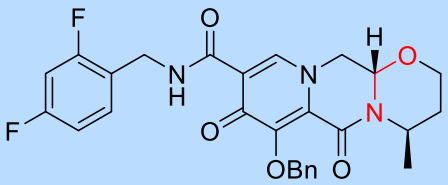


dolutegravir
IC_{50} = 1.7 nM
F = 34% (rat); 35% (dog); 25% (cyno)
$t_{1/2}$ = 14 h in humans





140 °C, μM: 81% yield
20:1 diastereoselectivity



- Hemiacetal OH increases activity against resistant mutants
- Cyclic aminals used to overcome stability issue with hemi-aminal lead
  - enantiomers resolved: equipotent
  - stable entity with no interconversion
- 1:1 mixture obtained with 3-aminopropanol; stereoselective synthesis not available
  - stereochemical control with chiral substituted 3-aminopropan-1-ol
- Substituted oxazinane analogs retained good activity and PK properties

"We were initially concerned that the hemiaminal stability would be an issue, but no interconversion or chemical stability issues were observed with the purified isomers"

T. Kawasuji *et al*., *J. Med. Chem*., 2013, **56**, 1124-1135; B.A. Johns *et al*., *J. Med. Chem.,* 2013, **56**, 5901-5916;
Successful Strategies for the Discovery of Antiviral Drugs, M. Desai, N.A. Meanwell, Eds. RSC Publishing, Chapter 6.