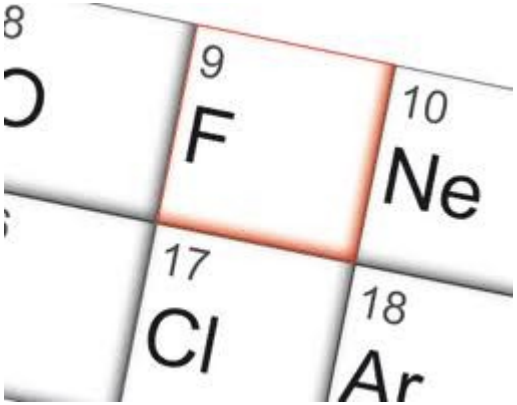
Fluorine in Medicinal Chemistry

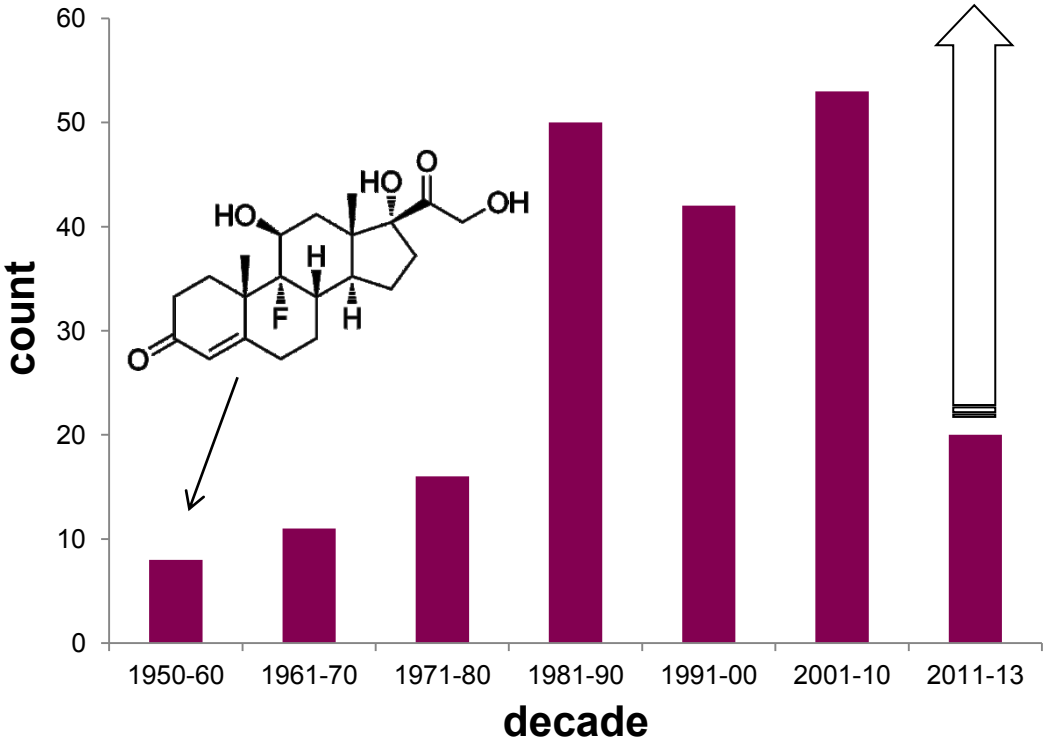


Steve Swallow

AstraZeneca

Historical Perspective

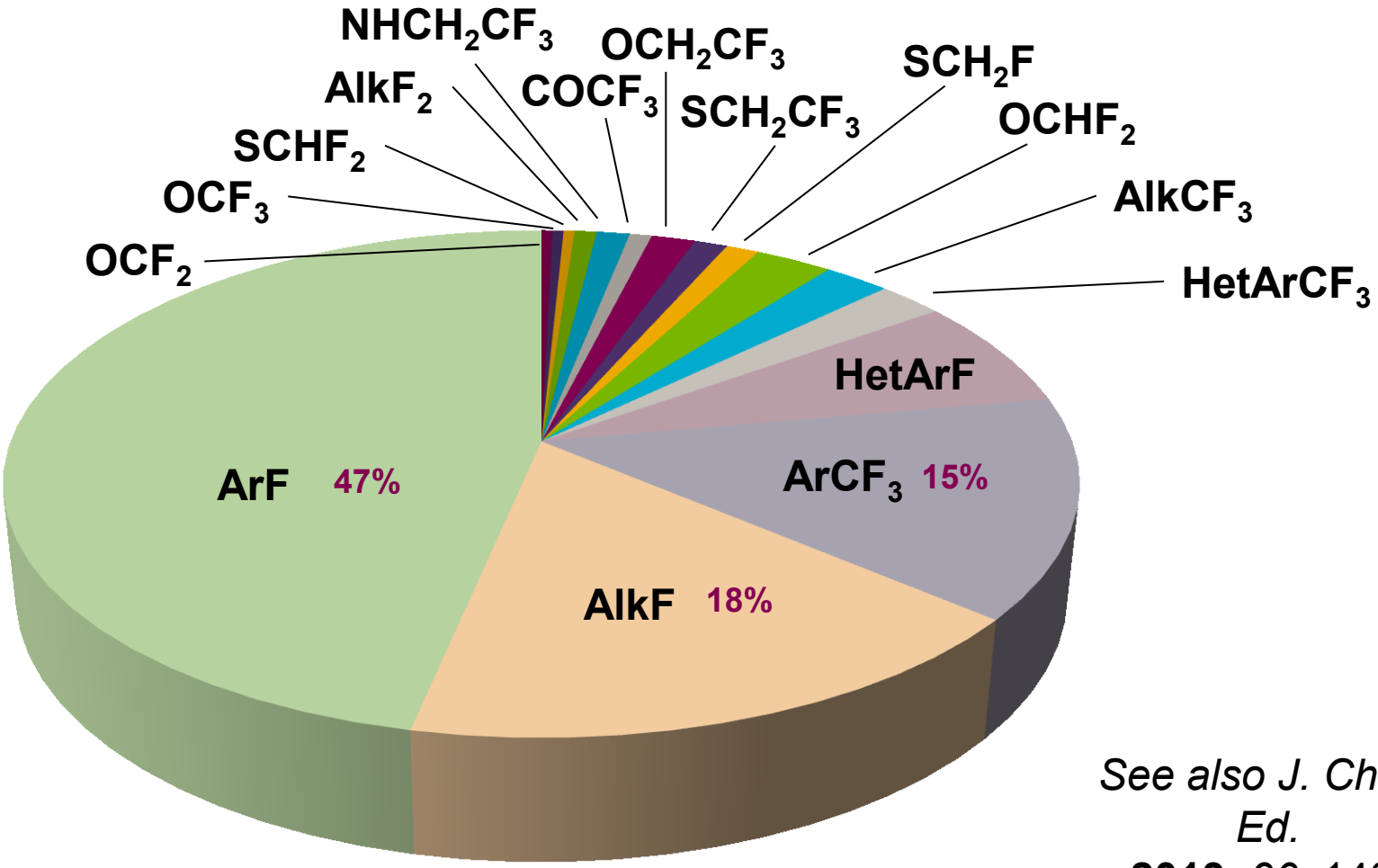
Henri Moissan



- Early use dominated by steroids & anesthetics
- 80's surge following development of DAST in 1970

~15% of marketed drugs contain at least one fluorine

Diversity of Fluorine Containing Pharmaceuticals

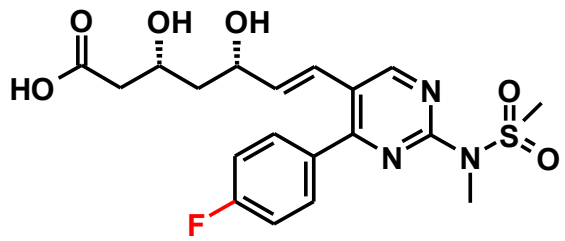


See also J. Chem. Ed. **2013**, *90*, 1403

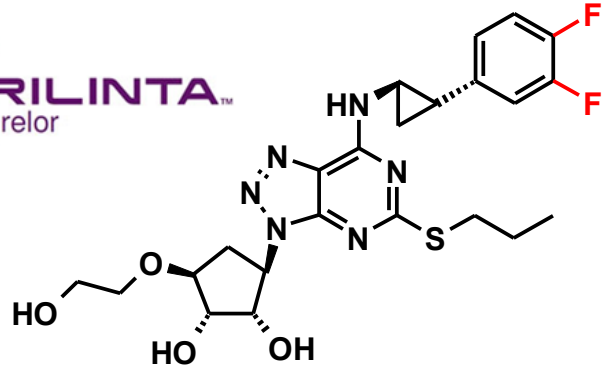
The use of fluorine is still dominated by a few chemotypes

Fluorinated AstraZeneca Pharmaceuticals

CRESTOR®
rosuvastatin calcium

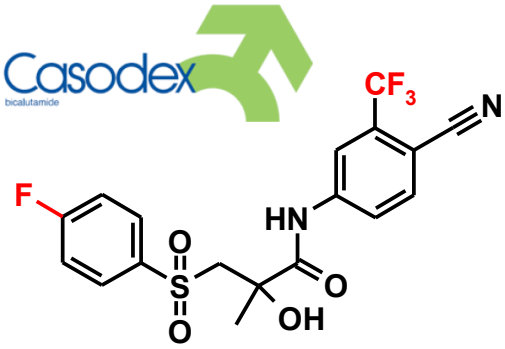


BRILINTA™
ticagrelor

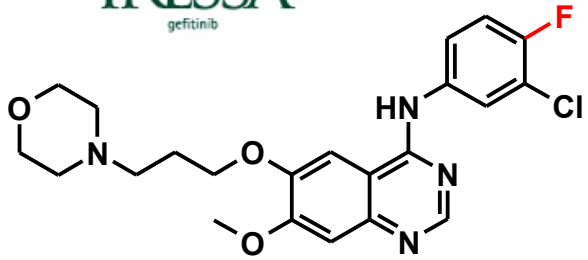


FASLODEX®
fulvestrant Injection

Casodex®
bicalutamide



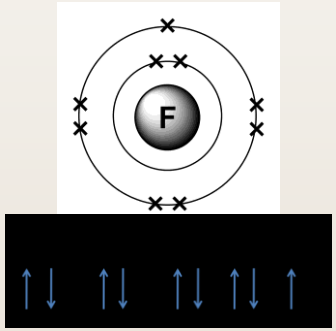
IRESSA®
gefitinib



The Special Nature of Fluorine

F as a substituent is:

- **Small**
- **Low MW = 19**
- **Highly electronegative**



The C-F bond is :

- **Very strong**
- **Highly polarised**
- **Has low energy σ***

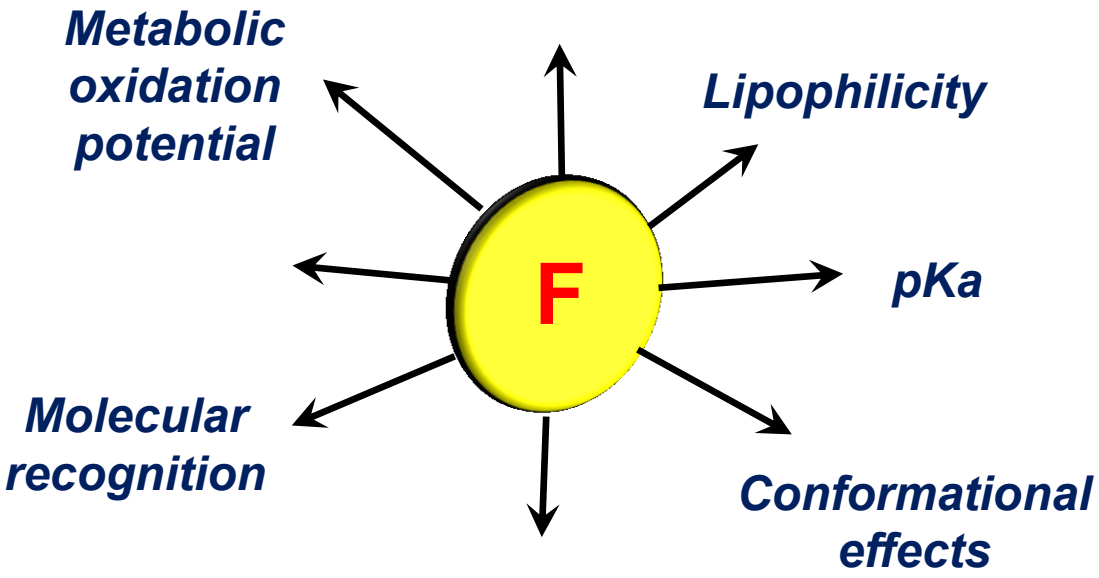
$$\overset{\delta+}{C}—\overset{\delta-}{F}$$

	H	C	N	O	F	Cl	Br
Van de Waals radius	1.2	1.7	1.55	1.52	**1.47**	1.75	1.85
Electronegativity	2.1	2.5	3	3.5	**4**	3.2	2.8
Bond strength to C	98	83	70	84	**105**	77	66

Uniquely, incorporation of fluorine introduces polar hydrophobicity

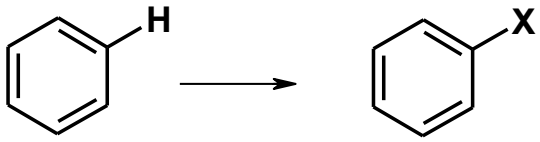
Influences of Fluorine in Medicinal Chemistry

- Powerful inductive electronic effects
- Electrostatic molecular interactions



F can influence potency, selectivity, absorption & metabolism

Impact of Fluorination on Lipophilicity



X	Π	σ_I
H	0.00	0.00
F	0.14	0.52
Cl	0.71	0.47
CH_3	0.56	0.04
CF_3	0.88	0.42
OCH_3	-0.02	0.29
OCF_3	1.04	0.39
SO_2CH_3	-1.63	0.48
SO_2CF_3	0.55	0.73

Ar-F

- Strong EWG & modest increase in logP
- Low risk, potentially high impact modification
  - **metabolic stability**
  - **potency**

Ar-CF_3

- Strong EWG & significant increase in logP

Ar-SO_2CF_3

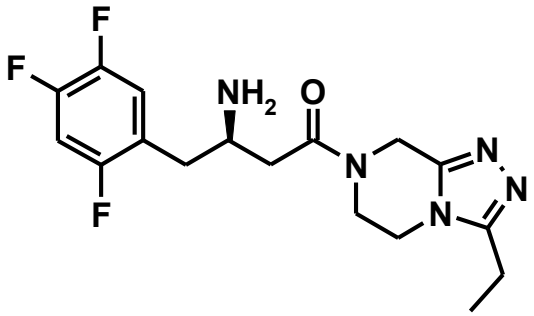
- Powerful EWG & large increase in logP
- 150x more lipophilic than SO_2Me!

Impact of Fluorination on logD & Permeability

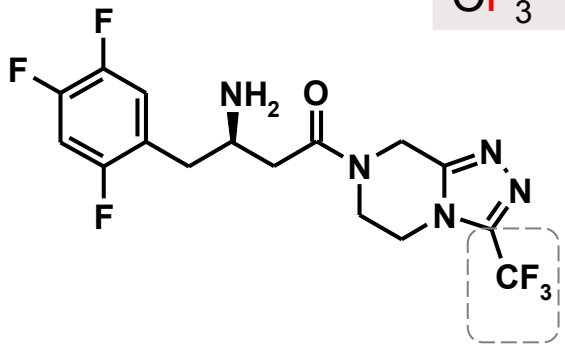
DPPIV inhibitors – *Sitagliptin (JANUVIA™)*

J. Med. Chem. **2005,** *48*, 141
Bioorg. Med. Chem. Lett. ***2007,*** *17*, 3373

X	Π
CH_2CH_3	1.02
CF_3	0.88



Clp (ml/min/kg)	$T_{1/2}$ (h)	F
70	1.7	2%



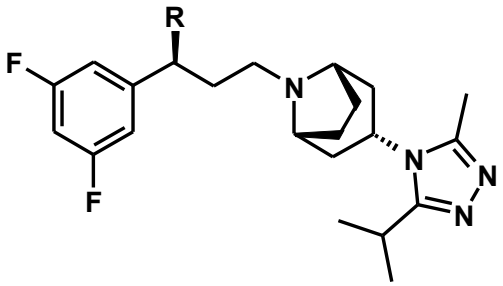
permeability

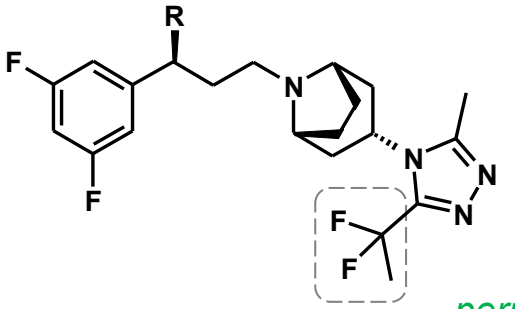
Clp (ml/min/kg)	$T_{1/2}$ (h)	F
60	1.7	76%

- Triazoles are excellent H-bond acceptors, strong dipole across heterocycle
- Improved absorption and bioavailability

Impact of Fluorination on LogD & Permeability

CCR5 antagonists - AstraZeneca





permeability

LogD	Clp (ml/min/kg)	$T_{1/2}$ (h)	F
1.8	16	3.9	9%

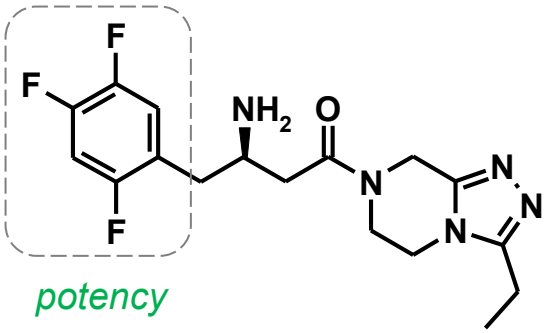
LogD	Clp (ml/min/kg)	$T_{1/2}$ (h)	F
2.5	6	3.9	68%

Significant influence of F on heterocycle properties

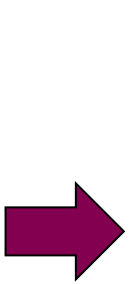
Impact of Fluorination on Permeability

DPPIV inhibitors – *Sitagliptin (JANUVIA™)*

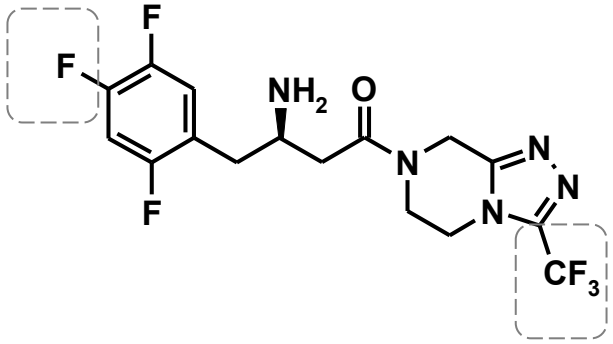
J. Med. Chem. **2005,** *48*, 141
Bioorg. Med. Chem. Lett. ***2007,*** *17*, 3373



potency



CV safety



permeability

LogD	Clp (ml/min/kg)	$T_{1/2}$ (h)	F
1.8	16	3.9	9%

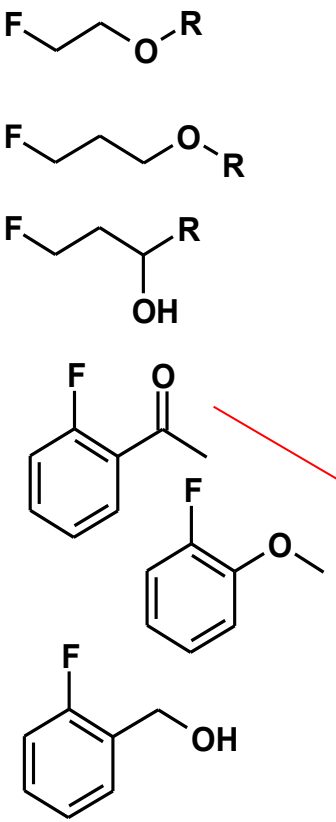
- Triazoles are excellent H-bond acceptors, strong dipole across heterocycle

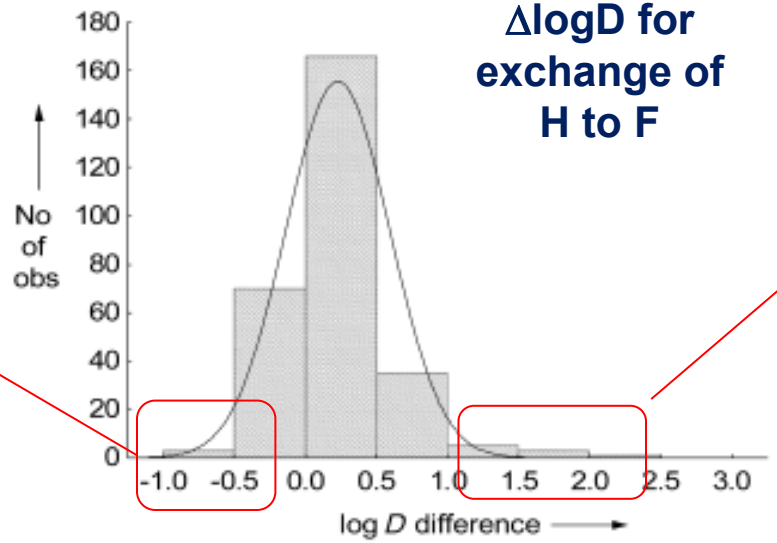
LogD	Clp (ml/min/kg)	$T_{1/2}$ (h)	F
2.5	6	3.9	68%

- Improved absorption and bioavailability

Impact of Fluorination on Lipophilicity

ChemBioChem **2004,** 5, 637





ΔlogD for exchange of H to F

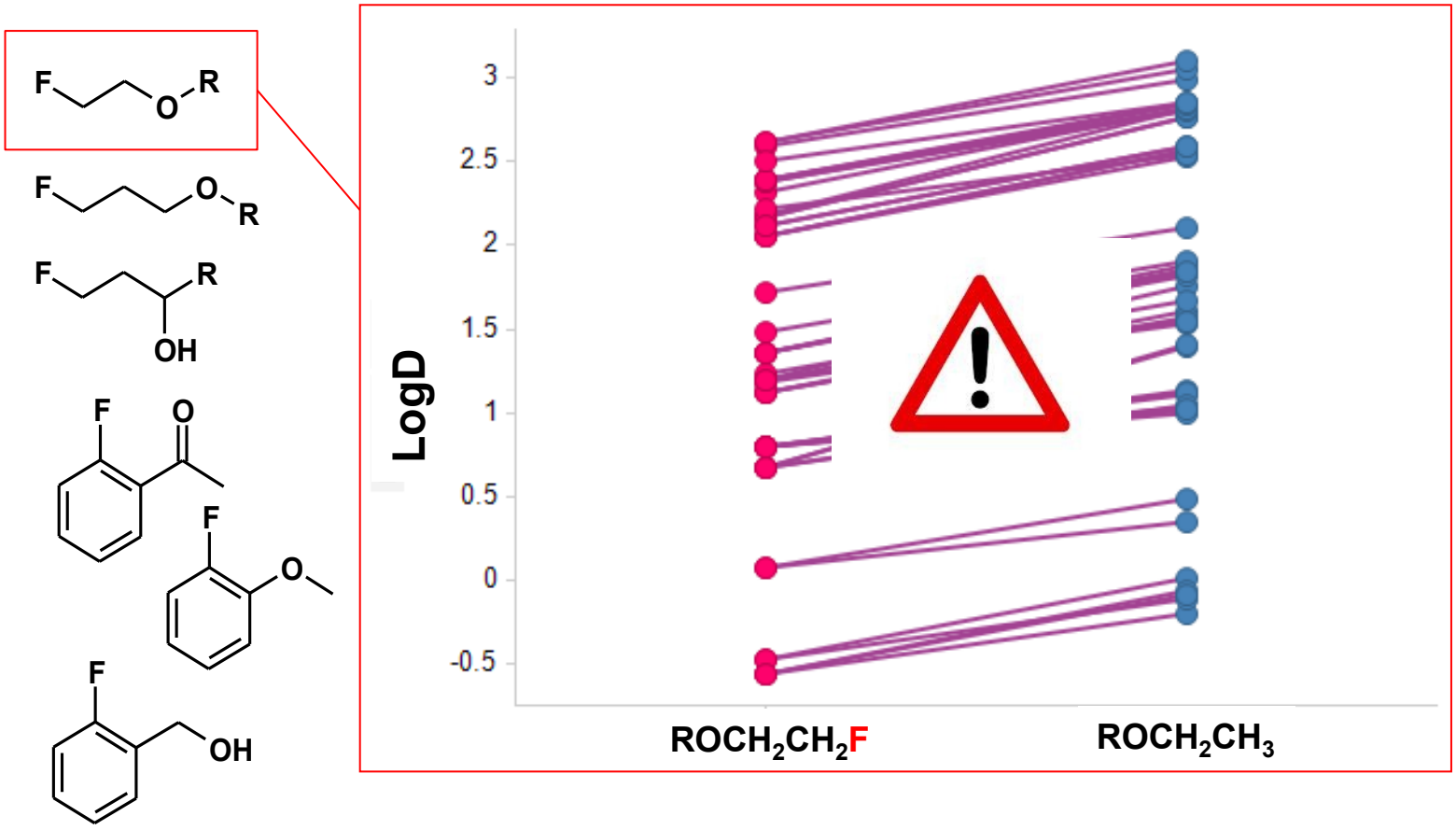
Impacts on pKa

↓

Additional effects on partitionining at pH 7.4

Increase in LogD not always true for F addition

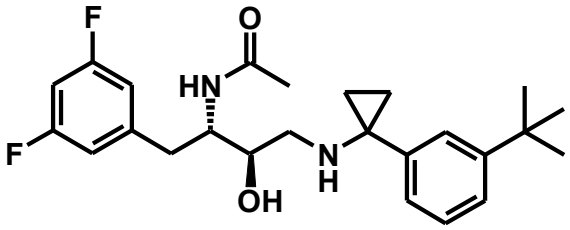
Impact of Fluorination on Lipophilicity



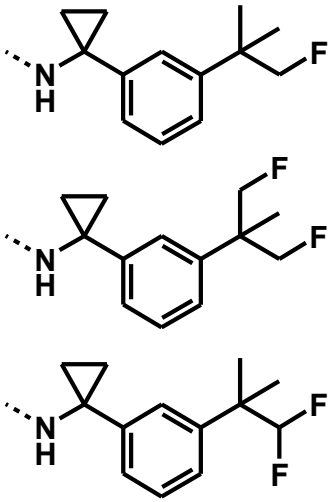
Increase in LogD not always true for F addition

Impact of Fluorination on Lipophilicity

Bioorg. Med. Chem. Lett. **2010**, 20, 6231

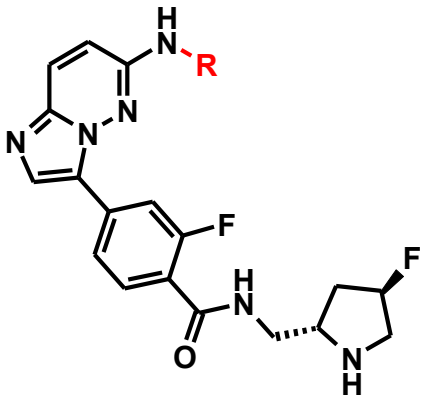


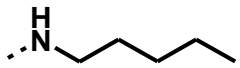
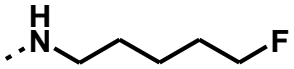
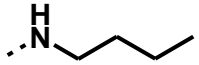
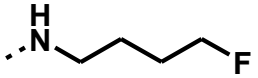
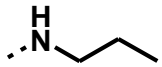
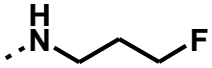
logD 4.6



	logD	
	4.1	Δ -0.5
	3.7	Δ -0.9
	4.0	Δ -0.6

Bioorg. Med. Chem. Lett. **2011**, 21, 4550



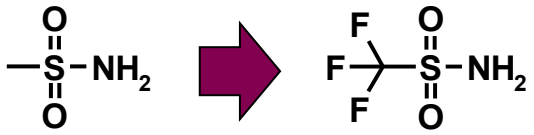
R =	logD	R =	logD	
	**4.1**		**3.3**	Δ -0.8
	**3.5**		**2.8**	Δ -0.7
	**3.1**		**2.5**	Δ -0.6

Aliphatic F addition can lead to reduced logD

Impact of Fluorination on pKa

Acids - Carbonic anhydrase II inhibitors

J. Biol. Chem. **1993**, 15, 26233

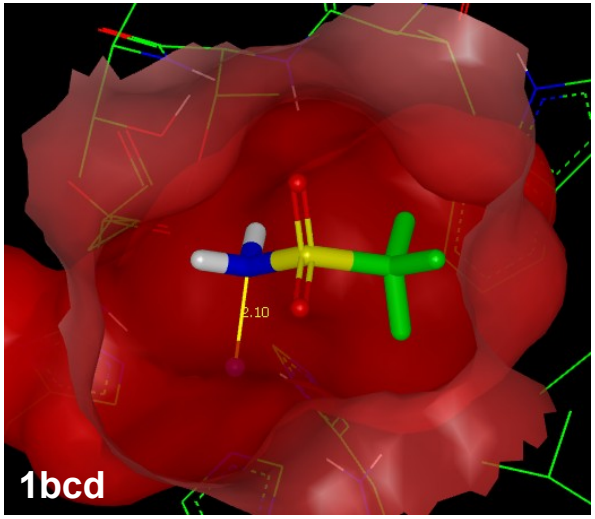


pK_a 10.5

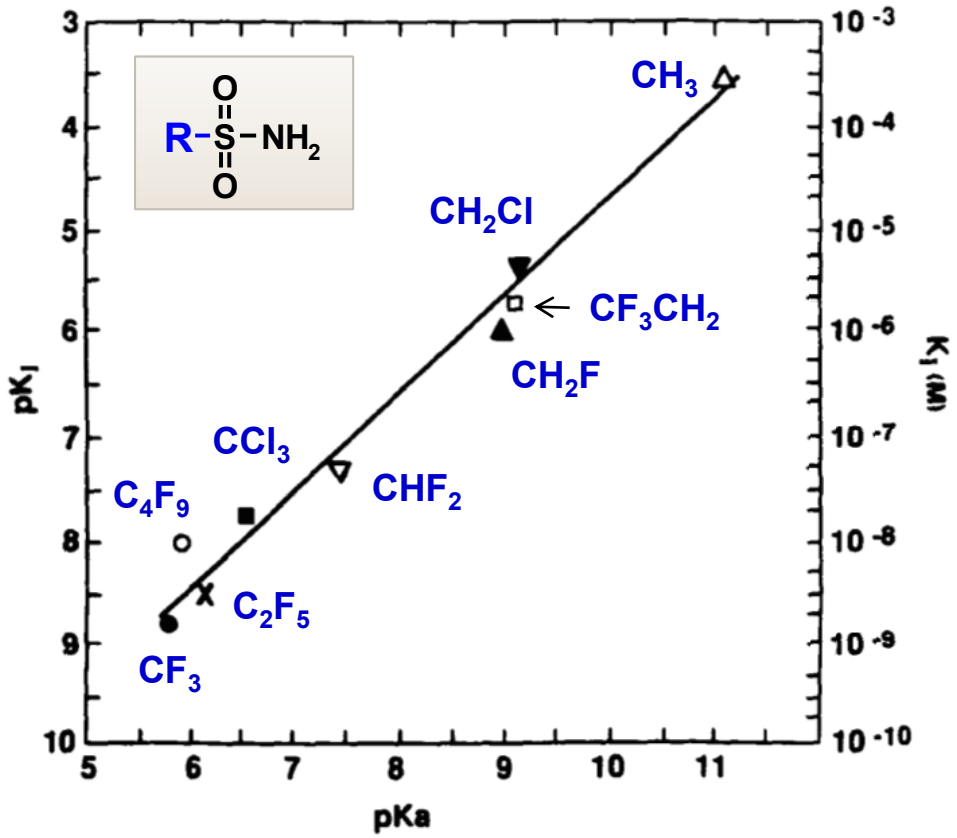
Ki = 320μM

pK_a 5.8

Ki = 2nM



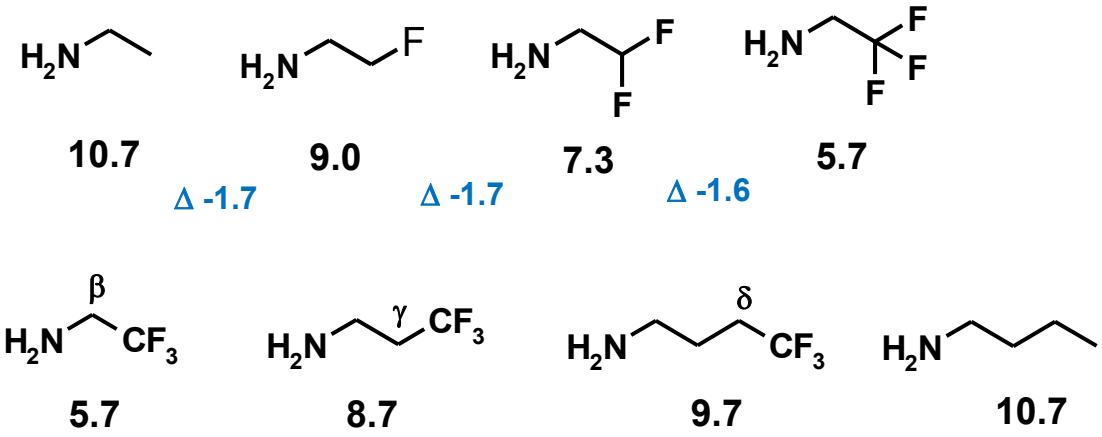
Linear Relation between Ki & pKa

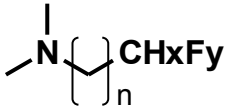


F substitution is a powerful tool for pKa modulation

Impact of Fluorination on pKa
Bases

ChemMedChem. **2007**, 2, 1100





n	ΔpKa
1	-1.7 / β-F
2	-0.7 / γ-F
3	-0.3 / δ-F
4	0.1 / ε-F

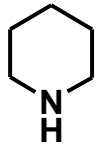
Generally predictable impact of F on basic pKa's

Impact of Fluorination on pKa

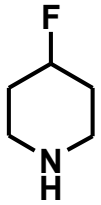
Bases

ChemMedChem. **2007**, 2, 1100

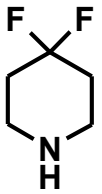
More complicated in ring systems – conformational effects



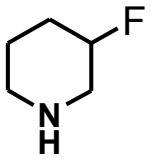
11.1



9.4

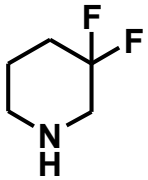


8.5



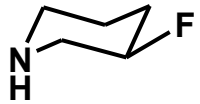
9.3

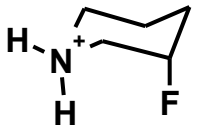
Expect 9.1
(Δ = -1.7 + -0.3 = -2.0?)



7.4

Expect 7.1





Axial F preferred in protonated form Contribution to higher than expected pKa's

Fluorine substitution can give rise to conformational effects too...

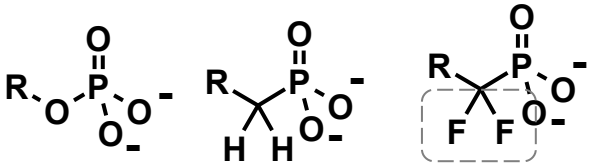
Impact of Fluorine on Conformation

Chem. Soc. Rev. **2008**, 37, 308

Geometry at carbon

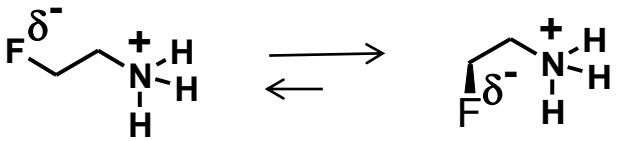
~111°

~116°

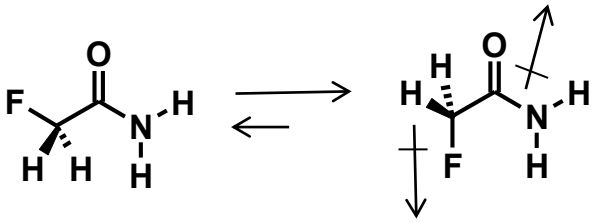


Better mimic

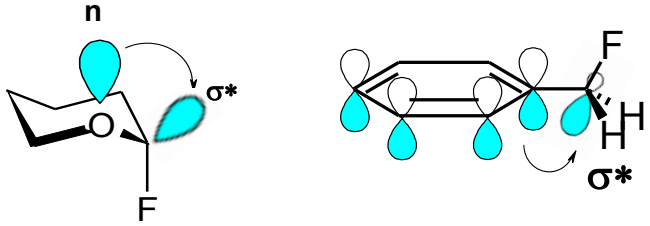
Charge-Dipole interactions



Dipole interactions



Hyperconjugation & σ* C-F



Other:

1,2 C-F bond attraction

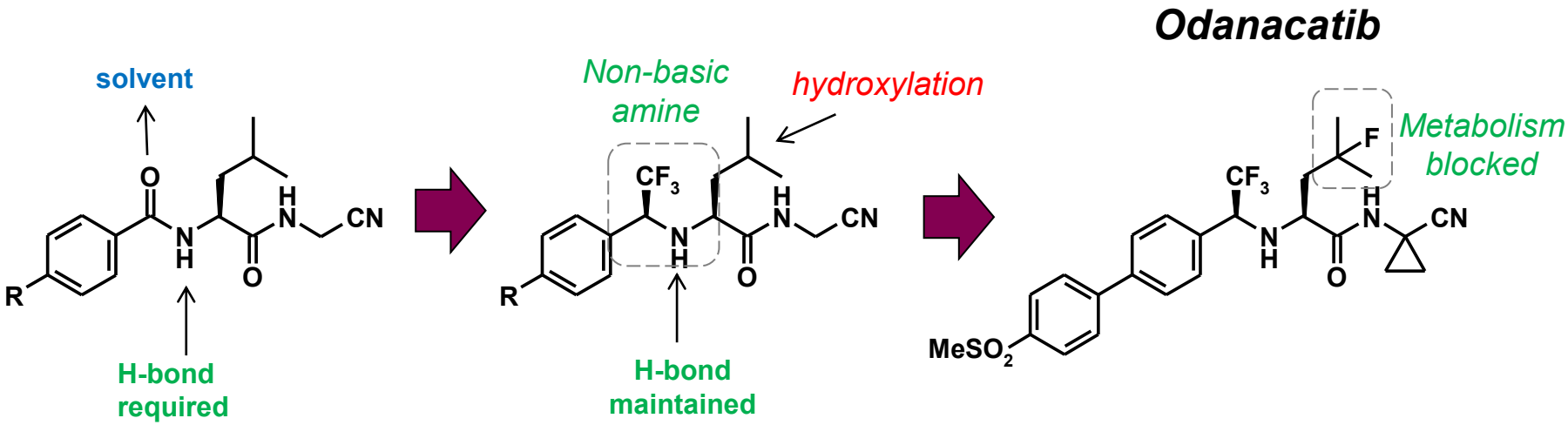
1,3 C-F bond repulsion

Impact of Fluorination on pKa

Example Cathepsin K inhibitors - *Odanacatib*

Chem. Eur. J., **2003**, *9*, 4510 Zanda

Bioorg. Med. Chem. Lett., **2008**, *18*, 923



- Peptidic nature

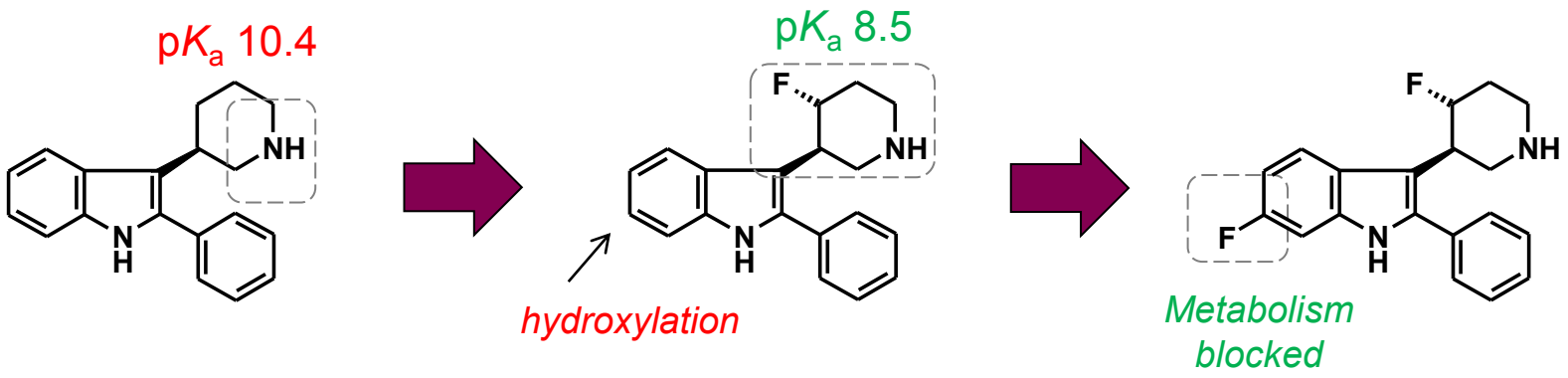
- 10-20x > potency
- Improved amide stability
- Short $t_{1/2}$ in cyno

- Improved metabolism
- Good selectivity

Amine can be rendered non-basic by Fluorine substitution

Impact of Fluorination on pKa
Example – $5HT_{2A}$ antagonists

J Med Chem. **2001**, *44*,1603



- Poor F%
- Ki = 0.99nM

- F = 18%
- Ki = 0.43nM

- F = 80%
- Ki = 0.06nM ~10x
  (Note Cl = 2.3nM)

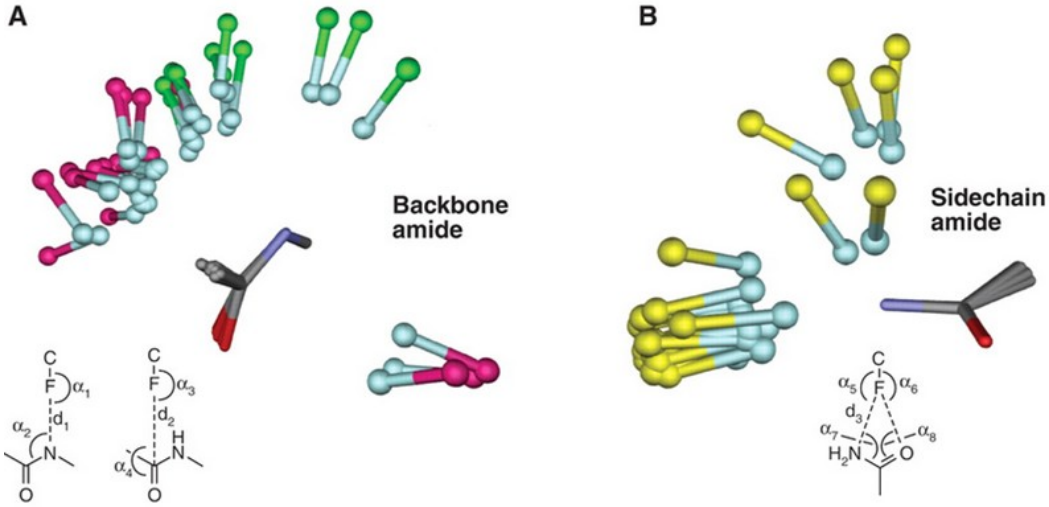
Absorption improved by pKa modulation with fluorine

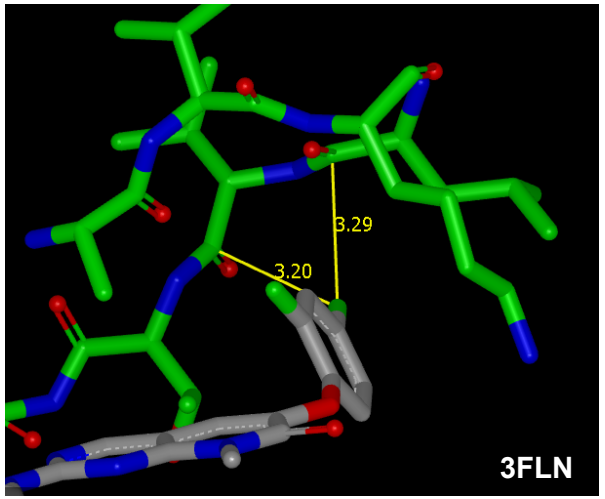
Intermolecular Interactions in Proteins

Science, **2007,** *317*, 1881

Dipole (δ+/δ-)...Dipole (δ+/ δ-)

- Observed interactions reflect that F not a good H-bond acceptor
  - But: C-F dipole undergoes 'multipolar interactions' – to amide N-H, backbone C=O, C-H and guainidinium groups
  - Can provide some potency benefit beyond lipophilicity



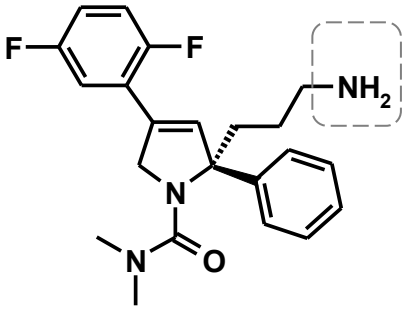


J. Med. Chem. **2011,** 54, 2255

Specific interactions dominated by dipole-dipole interactions

Impact of Fluorination on pKa
Example - KSP inhibitors

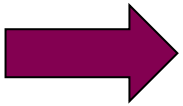
Bioorg. Med. Chem. Lett. **2007**, 17, 2697

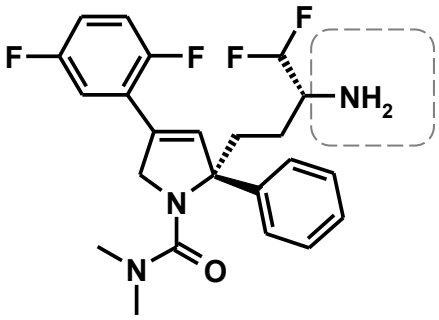


pK_a 10.3

Cellular Efflux

- MDR efflux ratio = 1000





pK_a 7.0

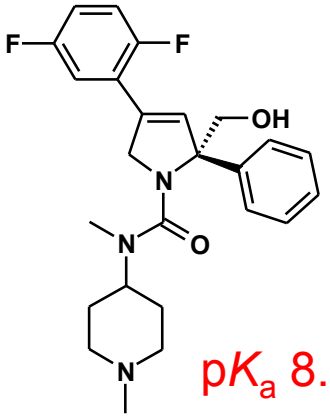
Reduced efflux

- MDR efflux ratio = 3

Cellular efflux improved by pKa modulation with fluorine

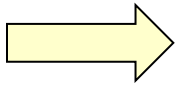
Caution in use of Fluoroethyl Amines & Ethers
Metabolism to toxic metabolites

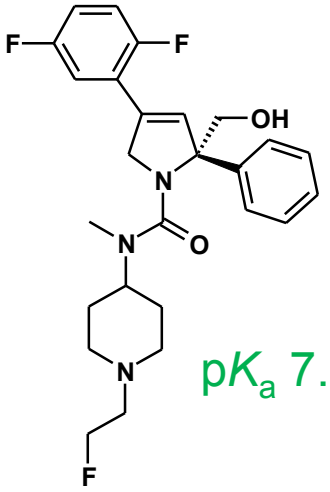
J. Med. Chem. **2008**, *51*, 4239



pK_a 8.8

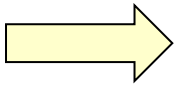
Desire to reduce pK_a to reduce efflux

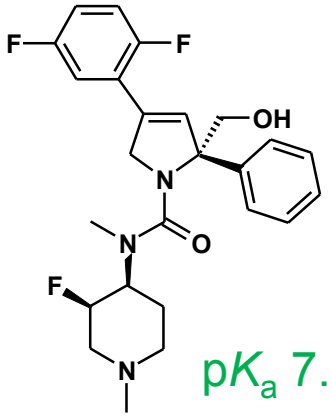




pK_a 7.6

"we were surprised to find mortality within 12 h postdose in 2 of 3 rats in the 12 mg/kg group."



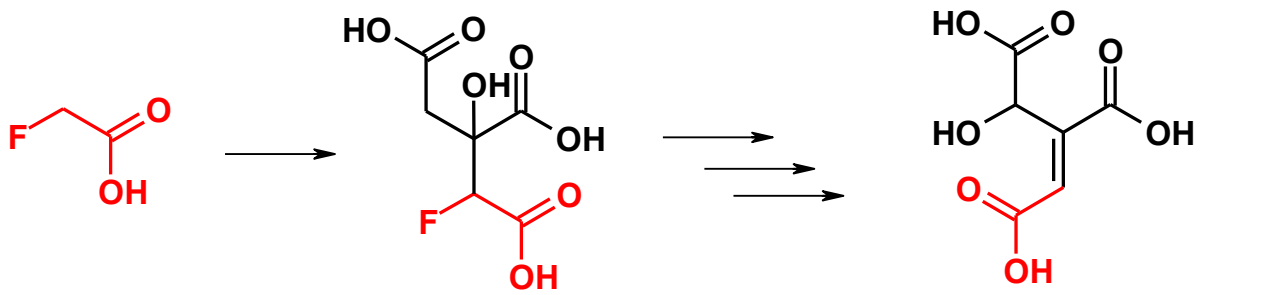


pK_a 7.6

Reflects AZ experience.
Consequence of increase focus on desirable physchem space?

Caution in use of Fluoroethyl Amines & Ethers
Metabolism to toxic metabolites

- Fluoroacetic acid is a known potent rodenticide and human toxin
  - Lethal in man in 2-10mg/kg doses
  - Dogs also particularly sensitive: LD_{50} 0.05-1mg kg
  - Mechanism well understood – inhibitor of tricarboxylic acid cycle



2-fluorocitrate

4-hydroxy-trans-aconitate
potent inhibitor of aconitase

- Described in Stryer in 1980's

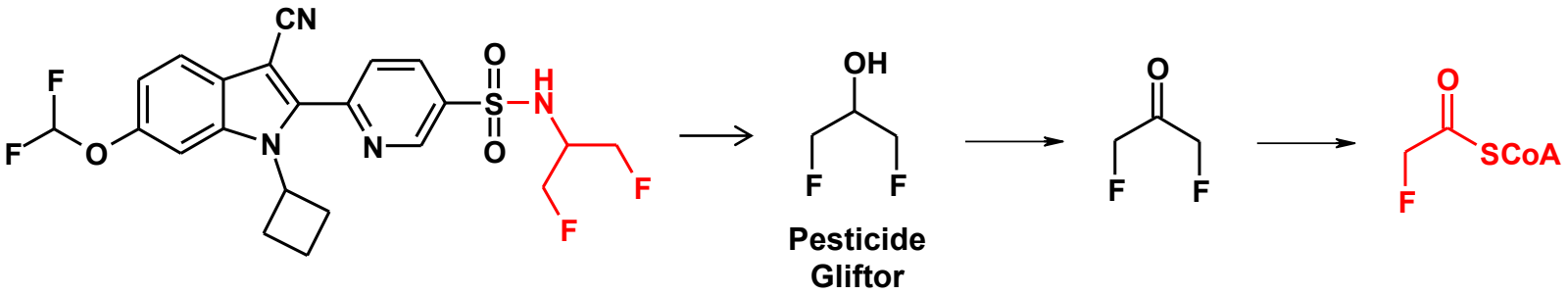
Caution in use of Fluoroethyl Amines & Ethers

Metabolism to toxic metabolites

Caution in use of Fluoroethyl Amines & Ethers
1,3-difluoroacetone

- Beware related compounds

J. Med. Chem. **2014** *asap*



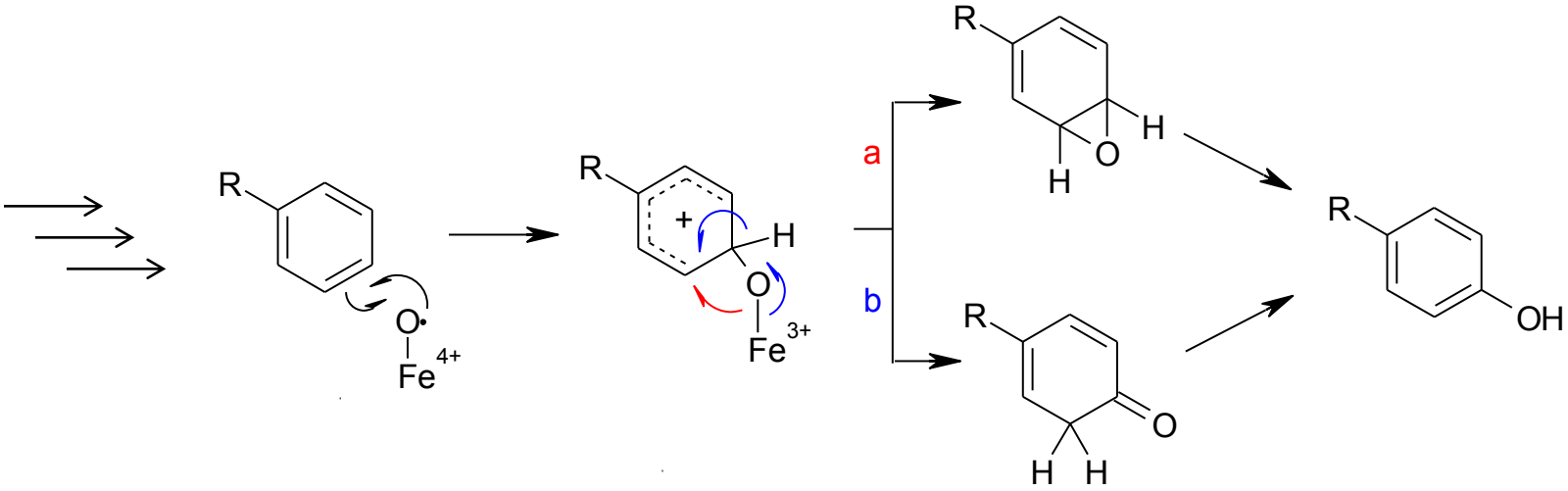
J. Biochem. Mol. Tox. **2001**, *15*, 47

Metabolite has predictable dose dependent toxicity – extent of metabolism unpredictable

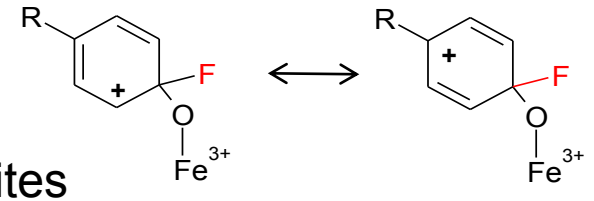
Fluorination to Reduce Metabolic Oxidation

Aromatic ring oxidation

Metabolic oxidation – a complex multistep process



- Appropriate F substitution can reduce intermediate carbocation stability via
  - Induction
  - Lack of resonance stabilisation.

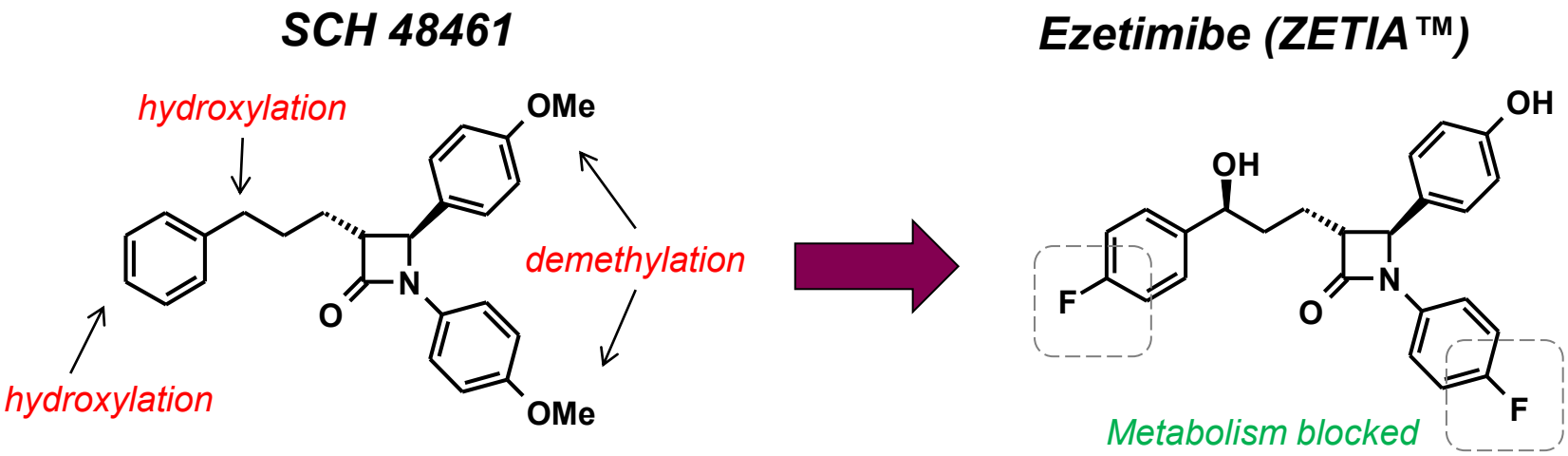


- May see oxidation switch to other positions & sites

Aromatic F to reduce metabolism or prevent bioactivation

Fluorination to Reduce Metabolic Oxidation

Example- *Ezetimibe (ZETIA™)*



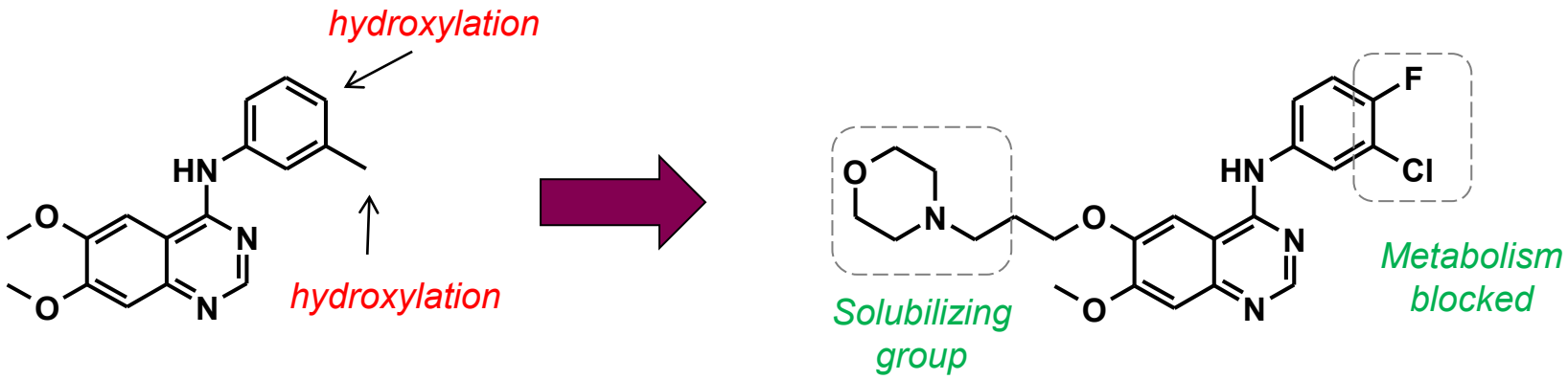
- Clinical proof of concept - modest effect
- Complex metabolite profile
  - **Retain positive metabolite features**
  - **Blocked undesirable oxidations**
- 50x potency increase in in-vivo efficacy model

Targeted use of Aromatic F to reduce metabolism

Fluorination to Reduce Metabolic Oxidation

Example - *Gefitinib (IRESSA™)*

Bioorg. Med. Chem. Lett. **2001,** *11*, 1911

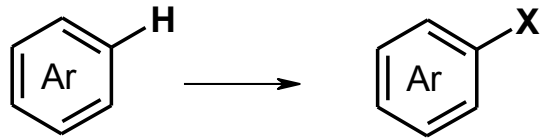


- Short half-life lead < 1hr
- High blood levels for 24h (po)

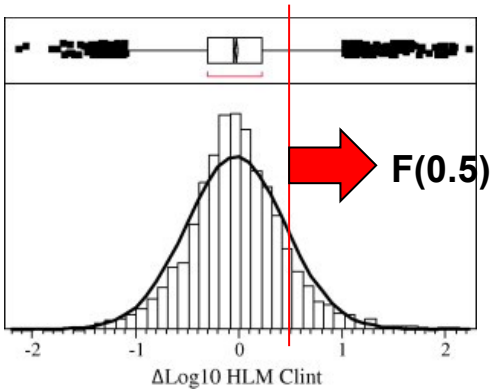
Targeted use of Aromatic F to reduce metabolism

Fluorination to Reduce Metabolic Oxidation
Molecular Matched Pairs – HLM Clint

Bioorg. Med. Chem. **2010**, 4405



$\Delta LogClint = Log_{10}Clint(Ar\text{-}H) - Log_{10}Clint(Ar\text{-}X)$



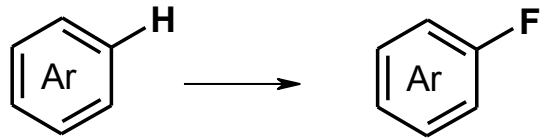
??

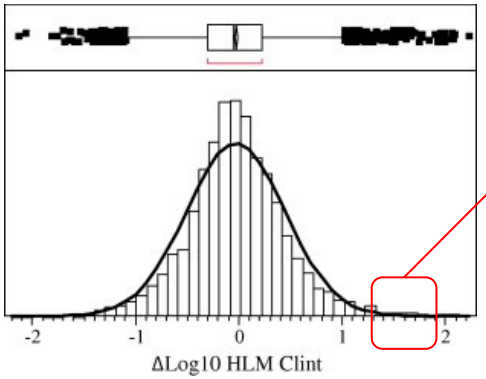
X	n	ΔLogClint (mean)	F(0.5)	ΔLogDa
4-F	497	0.06	0.086	0.18
4-CF_3	109	0.04	0.176	0.79
4-OCF_3	40	0.16	0.244	0.76
4-Me	181	-0.24	0.029	0.41
4-OCH_3	299	-0.10	0.073	0.03
4-Cl	337	0.01	0.079	0.57
4-CN	168	0.25	0.193	-0.28
4-SO_2Me	77	0.30	0.329	-1.12

Untargeted use of aromatic F mostly low impact on metabolism

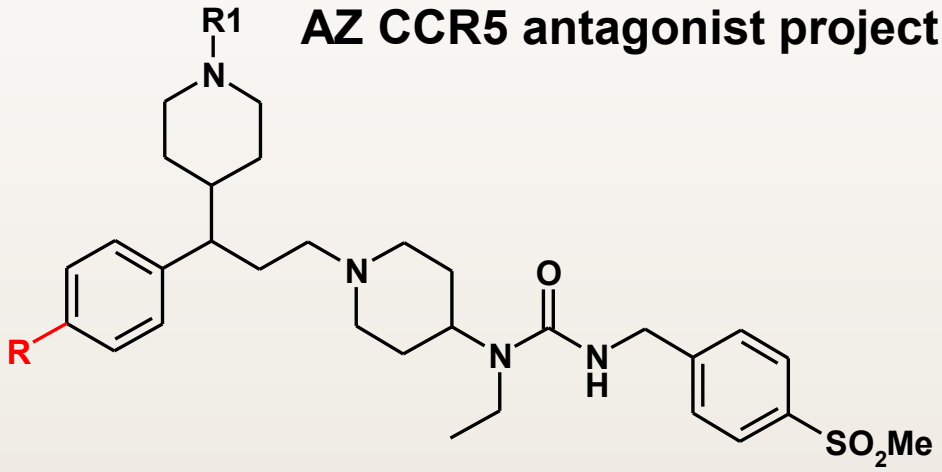
Fluorination to Reduce Metabolic Oxidation
Molecular Matched Pairs – HLM Clint

Bioorg. Med. Chem. **2010**, 4405





AZ CCR5 antagonist project



R = H **Clint >150**

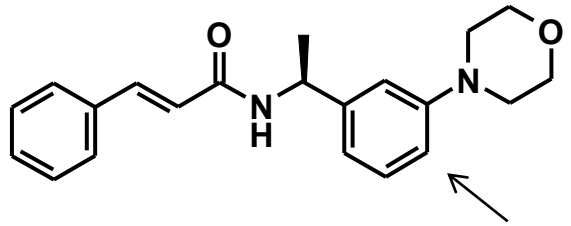
R = F **Clint = 5**

ΔLogClint >1.4

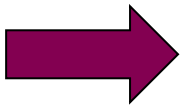
Targeted use of Aromatic F to reduce metabolism

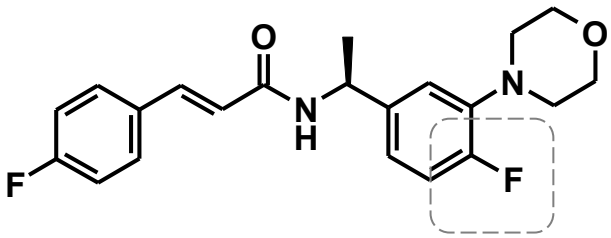
Fluorination to Prevent Metabolic Activation
Example - KCNQ2 potassium channel opener

J. Med. Chem. **2003,** *46,* 3778



hydroxylation





Metabolism blocked

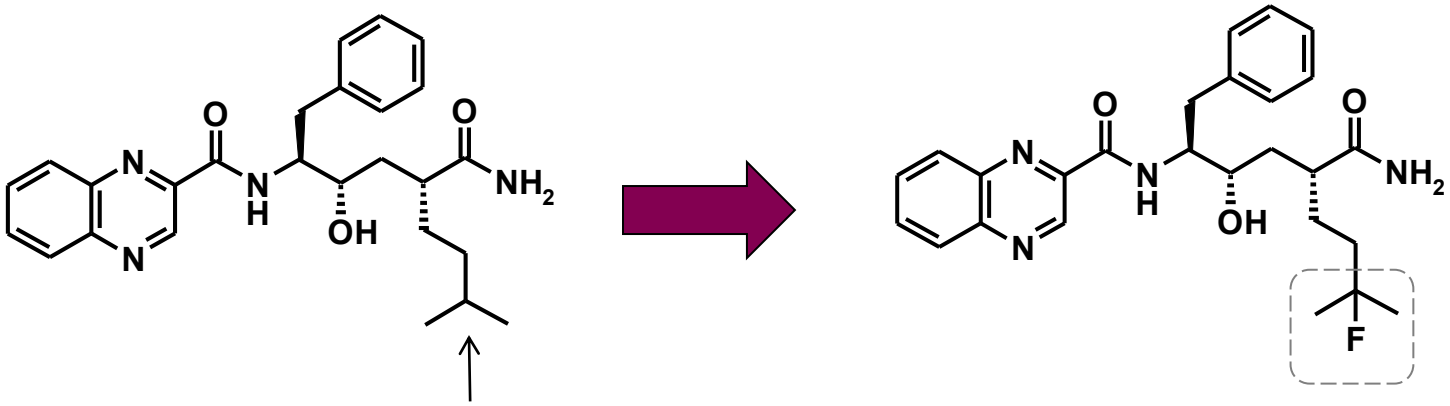
- Mechanism based Cyp3A4 inhibitor
- No Mechanism based Cyp3A4 inhibition

rationale

Targeted use of aromatic F to prevent bioactivation

Fluorination to Reduce Metabolic Oxidation
Aliphatic Oxidation - CCR1 antagonists

Bioorg. Med. Chem. Lett. **2004,** *14,* 2175



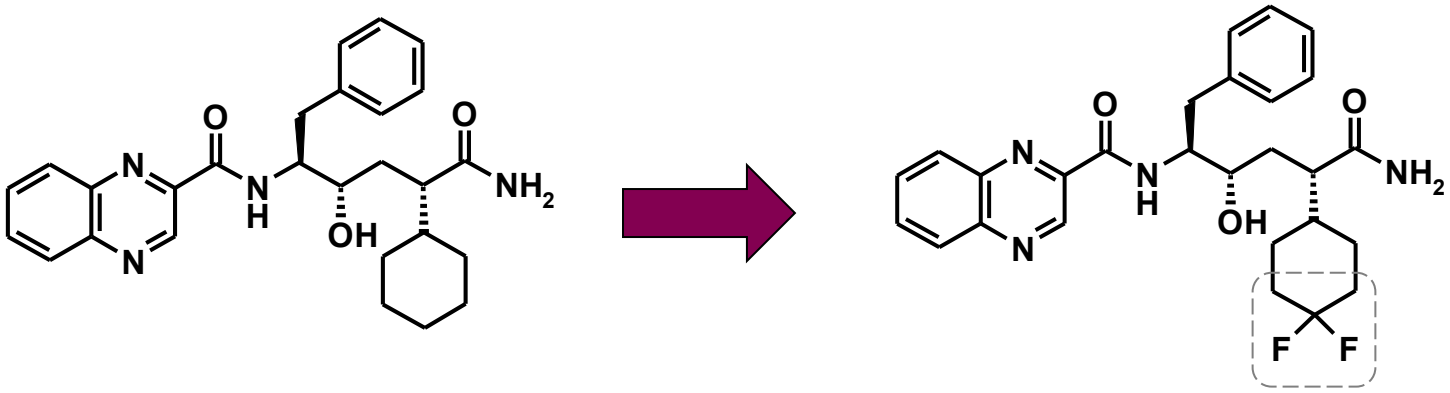
- HLM Clint (ml/min/kg) = 202
- CCL3 binding IC_{50} 28nM

- HLM Clint (ml/min/kg) = 8
- CCL3 binding IC_{50} 9nM

Targeted use of aliphatic F to reduce metabolism

Fluorination to Reduce Metabolic Oxidation
Aliphatic Oxidation - CCR1 antagonists

Bioorg. Med. Chem. Lett. **2004,** *14,* 2175



Metabolism blocked

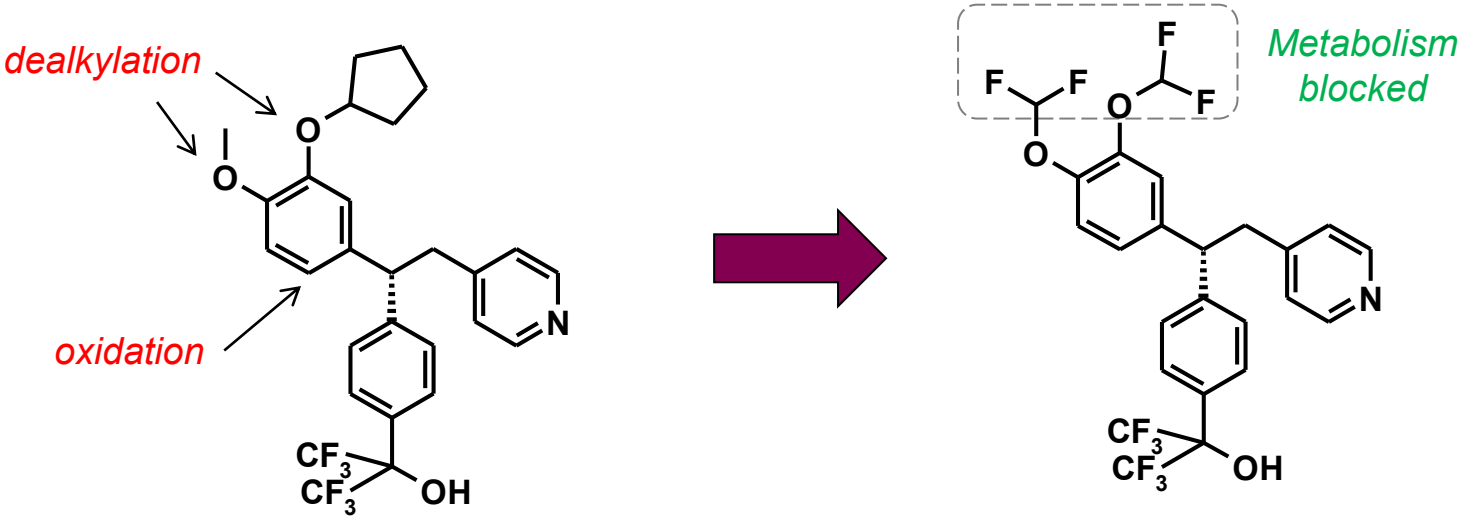
- HLM Clint (ml/min/kg) = 242
- CCL3 binding IC_{50} 8nM

- HLM Clint (ml/min/kg) = 35
- CCL3 binding IC_{50} 20nM

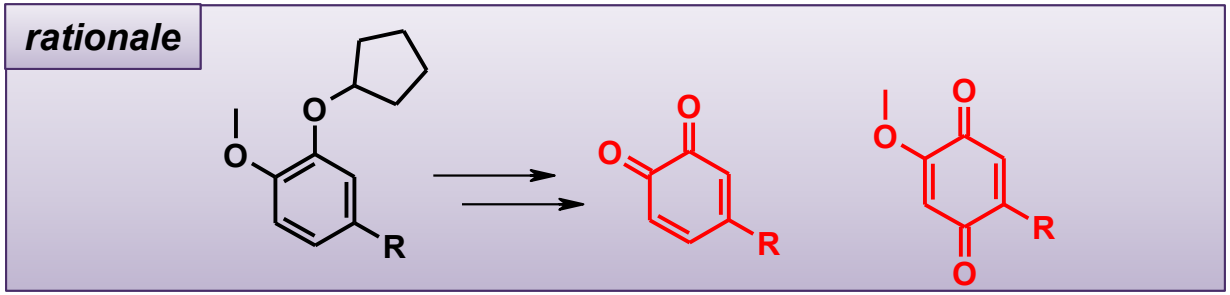
Targeted use of aliphatic F to reduce metabolism

Fluorination to Prevent Metabolic Activation
Example – PDEIV inhibitors

Bioorg. Med. Chem. Lett. **2002,** *12*, 2149



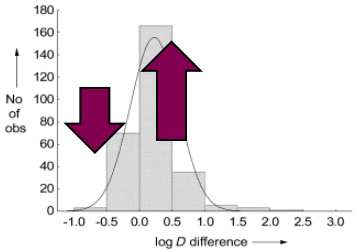
- Covalent binding
- No covalent binding



Targeted use of aliphatic F to prevent bioactivation

Summary

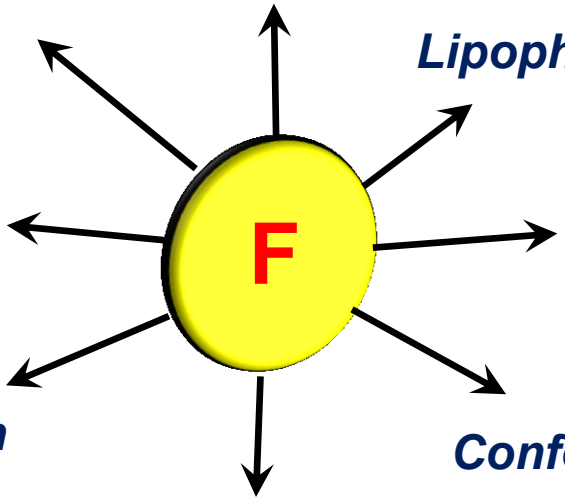
- Pharmaceuticals dominated by small number of chemotypes



- Targeted use to reduce Cl & metabolic activation

Metabolic oxidation potential

Lipophilicity



pKa

- Predictabl(ish)
- Can increase Clearance
- Beware cheap tricks

- Multipolar interactions dominate

Molecular recognition

Conformational effects

- Awareness

Easy access to fluorinated molecules & building blocks key to exploit unique properties