Fluorine in Medicinal Chemistry

Steve Swallow
Historical Perspective

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

~15% of marketed drugs contain at least one fluorine
The use of fluorine is still dominated by a few chemotypes.
Fluorinated AstraZeneca Pharmaceuticals
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 $\sigma^*$

Uniquely, incorporation of fluorine introduces polar hydrophobicity

<table>
<thead>
<tr>
<th></th>
<th>H</th>
<th>C</th>
<th>N</th>
<th>O</th>
<th>F</th>
<th>Cl</th>
<th>Br</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van de Waals radius</td>
<td>1.2</td>
<td>1.7</td>
<td>1.55</td>
<td>1.52</td>
<td>1.47</td>
<td>1.75</td>
<td>1.85</td>
</tr>
<tr>
<td>Electronegativity</td>
<td>2.1</td>
<td>2.5</td>
<td>3</td>
<td>3.5</td>
<td>4</td>
<td>3.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Bond strength to C</td>
<td>98</td>
<td>83</td>
<td>70</td>
<td>84</td>
<td>105</td>
<td>77</td>
<td>66</td>
</tr>
</tbody>
</table>
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

![Chemical structure](image)

<table>
<thead>
<tr>
<th>X</th>
<th>Π</th>
<th>σ₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>F</td>
<td>0.14</td>
<td>0.52</td>
</tr>
<tr>
<td>Cl</td>
<td>0.71</td>
<td>0.47</td>
</tr>
<tr>
<td>CH₃</td>
<td>0.56</td>
<td>0.04</td>
</tr>
<tr>
<td>CF₃</td>
<td>0.88</td>
<td>0.42</td>
</tr>
<tr>
<td>OCH₃</td>
<td>-0.02</td>
<td>0.29</td>
</tr>
<tr>
<td>OCF₃</td>
<td>1.04</td>
<td>0.39</td>
</tr>
<tr>
<td>SO₂CH₃</td>
<td>-1.63</td>
<td>0.48</td>
</tr>
<tr>
<td>SO₂CF₃</td>
<td>0.55</td>
<td>0.73</td>
</tr>
</tbody>
</table>

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

**Ar-CF₃**
- Strong EWG & significant increase in logP

**Ar-SO₂CF₃**
- Powerful EWG & large increase in logP
- 150x more lipophilic than SO₂Me!
Impact of Fluorination on logD & Permeability

DPPIV inhibitors – Sitagliptin (JANUVIA™)


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<td>CH₂CH₃</td>
<td>1.02</td>
</tr>
<tr>
<td>CF₃</td>
<td>0.88</td>
</tr>
</tbody>
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- Triazoles are excellent H-bond acceptors, strong dipole across heterocycle
- Improved absorption and bioavailability
Impact of Fluorination on LogD & Permeability

CCR5 antagonists - AstraZeneca

Significant influence of F on heterocycle properties
Impact of Fluorination on Permeability

DPPIV inhibitors – Sitagliptin (JANUVIA™)


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

<table>
<thead>
<tr>
<th>LogD</th>
<th>Clp (ml/min/kg)</th>
<th>$T_{1/2}$ (h)</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8</td>
<td>16</td>
<td>3.9</td>
<td>9%</td>
</tr>
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</table>

- Improved absorption and bioavailability

<table>
<thead>
<tr>
<th>LogD</th>
<th>Clp (ml/min/kg)</th>
<th>$T_{1/2}$ (h)</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>6</td>
<td>3.9</td>
<td>68%</td>
</tr>
</tbody>
</table>
Impact of Fluorination on Lipophilicity


Increase in LogD not always true for F addition

Impacts on pKa

Additional effects on partitionining at pH 7.4

ΔlogD for exchange of H to F
Impact of Fluorination on Lipophilicity

Increase in LogD not always true for F addition
Impact of Fluorination on Lipophilicity


![Chemical structure 1](image1)

$\text{logD} = 4.6$


\[
\begin{align*}
\text{R} & = & \text{logD} \\
\text{R} = & \begin{aligned}
\text{N} & \text{H} \\
\text{F} & \text{F}
\end{aligned} & \begin{aligned}
\text{logD} = & 4.1 \\
\text{logD} = & 3.7 \\
\text{logD} = & 4.0
\end{aligned}
\end{align*}
\]

$\text{Δ } -0.5$

$\text{Δ } -0.9$

$\text{Δ } -0.6$

Aliphatic F addition can lead to reduced logD
Impact of Fluorination on pKa
Acids - Carbonic anhydrase II inhibitors

J. Biol. Chem. 1993, 15, 26233

\[
\begin{align*}
\text{SO} & \quad \text{NH}_2 \\
\text{SO} & \quad \text{NH}_2 \quad \text{F} \quad \text{SO} \quad \text{NH}_2
\end{align*}
\]

\[pK_a \quad 10.5 \quad pK_a \quad 5.8\]

\[\text{Ki} \quad 320 \mu M \quad \text{Ki} \quad 2 \text{nM}\]

F substitution is a powerful tool for pKa modulation
Impact of Fluorination on pKa Bases

*ChemMedChem*. **2007**, 2, 1100

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

Fluorine substitution can give rise to conformational effects too...
Impact of Fluorine on Conformation

Chem. Soc. Rev. 2008, 37, 308

Geometry at carbon

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{F} & \quad \text{F} \\
\text{R} & \quad \text{R}
\end{align*}
\]

\[\sim 111^\circ \quad \sim 116^\circ\]

Charge-Dipole interactions

\[
\begin{align*}
\text{F} & \quad \text{δ}^- \quad \text{N} \quad \text{H} \\
\text{H} & \quad \text{N} \\
\text{O} & \quad \text{H} \\
\end{align*}
\]

Dipole interactions

\[
\begin{align*}
\text{F} & \quad \text{δ}^- \quad \text{N} \quad \text{H} \\
\text{H} & \quad \text{N} \\
\text{O} & \quad \text{H} \\
\end{align*}
\]

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


- 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

• 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 guanidinium groups
  - Can provide some potency benefit beyond lipophilicity

Specific interactions dominated by dipole-dipole interactions

Dipole (δ+/δ-)...Dipole (δ+/ δ-)

J. Med. Chem. 2011, 54, 2255
Impact of Fluorination on pKa
Example - KSP inhibitors


- MDR efflux ratio = 1000
- MDR efflux ratio = 3

Cellular efflux improved by pKa modulation with fluorine
Caution in use of Fluoroethyl Amines & Ethers
Metabolism to toxic metabolites


```
Pf  F
F

F

N
O
F
N
OH

N
O
F
F
pK_a 8.8

Desire to reduce pK_a to reduce efflux

```

```
Pf  F
F

F

N
O
F
N
OH

N
O
F
F

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.”

```

```
Pf  F
F

F

N
O
F
N
OH

N
O
F
F

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: \( \text{LD}_{50} \) 0.05-1mg kg
  - Mechanism well understood – inhibitor of tricarboxylic acid cycle

\[
\begin{align*}
\text{F} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\end{align*}
\]

2-fluorocitrate

\[
\begin{align*}
\text{F} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\end{align*}
\]

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

Warning 1080 Poison

Sodium fluoroacetate

will be present on the ground from: 6/8/07.

• DO NOT touch bait
• WATCH CHILDREN at all times
• DO NOT EAT animals from this area
• Poison baits or carcasses are DEADLY to DOGS

For more information contact:

Unauthorised removal of signs or baits is an offence.
Caution in use of Fluoroethyl Amines & Ethers

1,3-difluoroacetone

• Beware related compounds

\[ \text{J. Med. Chem. 2014 asap} \]

\[ \text{J. Biochem. Mol. Tox. 2001, 15, 47} \]

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™)


- 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


\[ \Delta \text{LogClint} = \log_{10} \text{Clint}(Ar-H) - \log_{10} \text{Clint}(Ar-X) \]

<table>
<thead>
<tr>
<th>X</th>
<th>n</th>
<th>( \Delta \text{LogClint} ) (mean)</th>
<th>F(0.5)</th>
<th>( \Delta \text{LogDa} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-F</td>
<td>497</td>
<td>0.06</td>
<td>0.086</td>
<td>0.18</td>
</tr>
<tr>
<td>4-CF(_3)</td>
<td>109</td>
<td>0.04</td>
<td>0.176</td>
<td>0.79</td>
</tr>
<tr>
<td>4-OCF(_3)</td>
<td>40</td>
<td>0.16</td>
<td>0.244</td>
<td>0.76</td>
</tr>
<tr>
<td>4-Me</td>
<td>181</td>
<td>-0.24</td>
<td>0.029</td>
<td>0.41</td>
</tr>
<tr>
<td>4-OCH(_3)</td>
<td>299</td>
<td>-0.10</td>
<td>0.073</td>
<td>0.03</td>
</tr>
<tr>
<td>4-Cl</td>
<td>337</td>
<td>0.01</td>
<td>0.079</td>
<td>0.57</td>
</tr>
<tr>
<td>4-CN</td>
<td>168</td>
<td>0.25</td>
<td>0.193</td>
<td>-0.28</td>
</tr>
<tr>
<td>4-SO(_2)Me</td>
<td>77</td>
<td>0.30</td>
<td>0.329</td>
<td>-1.12</td>
</tr>
</tbody>
</table>

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

Targeted use of Aromatic F to reduce metabolism
Fluorination to Prevent Metabolic Activation
Example - KCNQ2 potassium channel opener

J. Med. Chem. 2003, 46, 3778

- Mechanism based Cyp3A4 inhibitor
- No Mechanism based Cyp3A4 inhibition

Targeted use of aromatic F to prevent bioactivation
Fluorination to Reduce Metabolic Oxidation

Aliphatic Oxidation - CCR1 antagonists


- 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


- 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


- 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

- Multipolar interactions dominate

- Metabolic oxidation potential

- Lipophilicity

- Molecular recognition

- Conformational effects

- pKa

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

- Awareness

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