DISCOVERY SERVICES

Medicinal Chemistry Reference Sheet

Bond Lengths and Distances Angstroms Å			
C-H	1.09	C-O	1.43
C-C	1.54	C=O	1.20
C-N	1.47	C=C	1.34
C-S	1.92	O-H	0.96
C-F	1.40	H-H	0.74
C-Cl	1.77	C=O••H-O	2.7-3.0
C-Br	1.94	C=O••H-N	1.5-2.5
C-I	2.14	π stack C-C	3.3-4.3
N-H	1.01	Edge-to-face C-C	3.7-4.7

van der Waals Radii Angstroms Å	
H	1.20
C	1.70
N	1.55
O	1.52
F	1.35
Cl	1.75
Br	1.85
S	1.80
P	1.90

% Ionization at pH7.4			
Acid		Base	
pKa	%	pKa	%
4.4	99.9	4.4	0.1
5.4	99	5.4	1
6.4	90	6.4	10
7.4	50	7.4	50
8.4	10	8.4	90
9.4	1	9.4	99
10.4	0.1	10.4	99.9

Solubility Conversions

mg/mL → µmol

(value / Mw)
*1,000,000

µmol → mg/mL

(value x Mw)
/1,000,000

Ligand Efficiency (LE): ΔG/HAC = -1.4 LogKi/HAC				
Ki(nM)	Mw 300	400	450	500
10000	0.19	0.14	0.13	0.11
1000	0.37	0.28	0.26	0.23
100	0.43	0.33	0.30	0.26
10	0.49	0.38	0.34	0.30
1	0.56	0.42	0.38	0.34

Binding Energy		
Ki (nM)	-LogKi	ΔG
10000	5	-7.0
1000	6	-8.4
100	7	-9.8
10	8	-11.2
1	9	-12.6

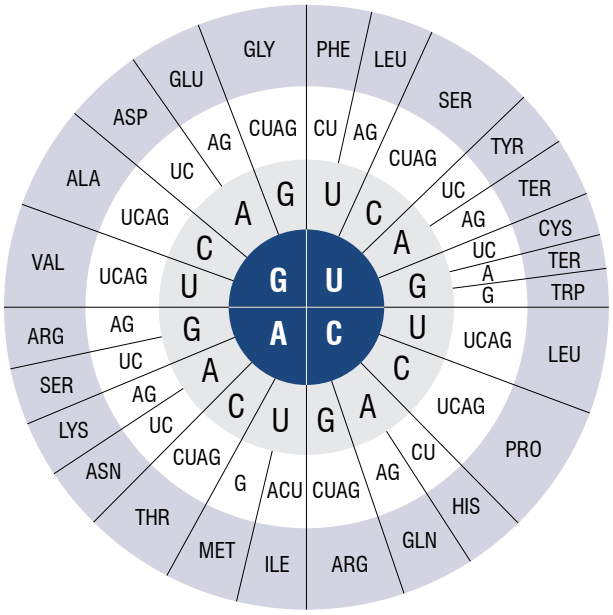
IC_{50}(nM)	pIC_{50}
1000	6.0
100	7.0
30	7.5
10	8.0
1	9.0

Gibbs Free Energy

$\Delta G = \Delta H - T\Delta S$

$\Delta G = -1.4\ LogKi$

1 kcal = -4.18kJ



Amino Acids		
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

Physiological Fluid pH	
Saliva	6.4
Stomach	1-3
Small intestine	5.5-7
Blood	7.4
Urine	5.8

Approx. Volumes (L/kg)	
Total body water	0.60
Intracellular fluid	0.34
Extracellular fluid	0.26
Blood	0.07
Plasma	0.04

Properties Favoring Oral Absorption (Lipinski)	
H-bond acceptors	<10
H-bond donors	<5
PSA	<140
Mw	<500
LogP	<5
Rotatable bonds	<10

Properties Favoring BBB Penetration	
H-bond total	<8
H-bond donors	<2
PSA	<70
Mw	<450
LogD	1-3
N+O atoms	<6

PK Parameters used in Drug Discovery		Units
AUC	Area under the concentration-time curve	ng.h/mL
Cl	Total clearance	mL/min/kg
V_d	Volume of distribution (apparent)	L/kg
$V_{d\ ss}$	Volume of distribution at steady state (apparent)	L/kg
$t_{½}$	Half life	h
MRT	Mean residence time (of a molecule in the body)	h
$F_{p.o}$	Bioavailability following oral administration	%
C_{max}	Maximum measured concentration	ng/mL
t_{max}	Time of maximum concentration	h
PPB	Plasma protein binding (% bound)	%
F_u	Fraction unbound (% unbound/100)	-
C_u	Concentration unbound (F_u x C_{total})	ng/mL

Species Parameters			Liver blood flow (mL/min/kg)	Glomerular filtration rate (mL/min/kg)
	Wt (kg)	Body Water (L)		
Mouse	0.02	0.015	90	14
Rat	0.25	0.17	60	5.2
Dog	10	6.0	31	6.1
Monkey	5	3.5	44	2.1
Human	70	42	21	1.8

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Impact of LogD on Drug-like Properties

LogD	Solubility	Cell permeability	Metabolism	V_d	$F_{p.o}$	BBB penetration	Renal clearance
<1	++++	+ (Paracelluar if Mw<200)	+	+	+	+	++++
1-3	++	++	++	++	++++	++++	+++
3-5	+	++++	++	++++	++	++	++
>5	+	++++	+++++	++++	+	+	+

Increasing Cell Permeability

- Remove ionizable groups
- Increase lipophilicity
- Replace polar groups with isosteres
- Reduce H-bonding
- Reduce polarity
- Reduce size and Mw
- Add non-polar side chain
- Convert to pro-drug

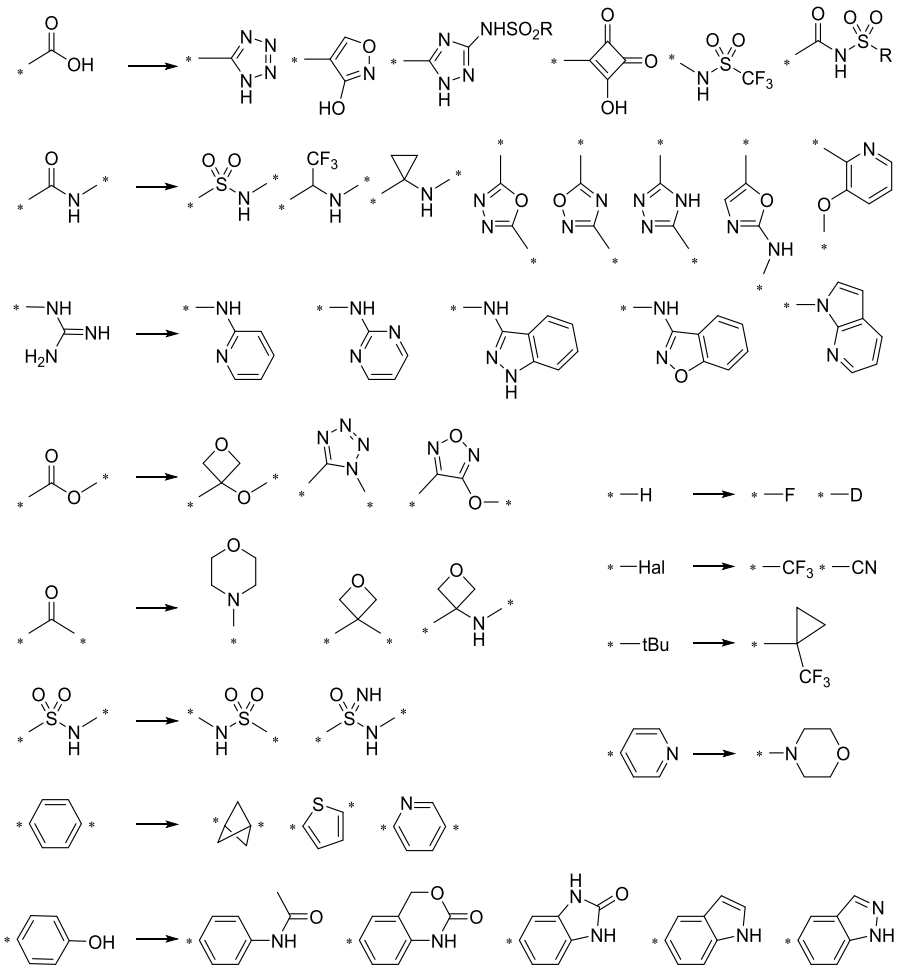
Increasing Solubility

- Add ionizable groups
- Reduce lipophilicity
- Add polar groups
- Add H-bond donors
- Reduce molecular weight
- Break aromatic co-planarity
- Increase 3D shape (fraction sp3)
- Convert to pro-drug

Reducing Phase I Metabolism

- Reduce lipophilicity
- Block sites of metabolism
- Modify labile functional groups
- Cyclization
- Modify ring size
- Invert chiral centers

Isosteres used in Medicinal Chemistry



Reducing Phase II Metabolism

- Block Phase I metabolism to phenols
- Introduce steric hindrance around site of Phase I metabolism
- Add electron withdrawing group near site of Phase I metabolism
- Replace phenols by isosteres

Reducing hERG Inhibition

- Reduce pKa of the amine
- Introduce steric bulk around amine
- Reduce lipophilicity
- Reduce aryl ring count
- Add an acidic group
- Introduce H-bond acceptors
- Rigidify structure

Increasing BBB Penetration

- Remove H-bond donors
- Replace external H-bonds by internal
- Reduce size and molecular weight
- Remove carboxylic acids
- Increase lipophilicity
- Reduce P-gp efflux
- Increase affinity for transporters

Increasing Dissolution Rate

- Reduce particle size
- Convert to a salt
- Pre-dissolve as oral solution
- Formulate with surfactant

Reducing PPB

- Reduce LogD
- Increase pKa of acidic groups
- Increase pKa of basic groups
- Increase polarity

Collaboration fosters innovation.

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