

# Basic Medicinal Chemistry Principles

$$LE = \frac{\Delta G}{\#heavy\ atoms} = \frac{-1.4 \log K_i}{\#heavy\ atoms}$$

0.25 - 0.35 = good hit, >0.35 potential development candidate

$$LipE = -\log K_i - cLogD \quad \text{or} \quad LipE = -\log K_i - cLogP$$

Use of experimental LogD preferred, 3-5 = good hit, >5 potential development candidate

$$LipMetE = LogD - Log(CL_{int,u}) \quad \text{Range} = -2 \text{ to } 2$$

Higher is better

## Binding Energy

Potency	-LogK <sub>i</sub>	ΔG
1 nM	9	-12.6
10 nM	8	-11.2
100 nM	7	-9.8
1 μM	6	-8.4

## Potency

10 fold = 1.4 kcal/mol

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

$$\Delta G = -1.4 \log K_i$$

$$1 \text{ kcal} = 4.18 \text{ kJ}$$

$$LogD = LogP - \gamma$$

Acid		Base	
pKa	γ	pKa	γ
3.4	4	7.4	0
4.4	3	8.4	1
5.4	2	9.4	2
6.4	1	10.4	3

## LE

K <sub>i</sub>	MWt			
	300	400	450	500
1 mM	0.19	0.14	0.13	0.11
1 μM	0.37	0.28	0.26	0.23
100 nM	0.43	0.33	0.30	0.26
10 nM	0.49	0.38	0.34	0.30
1 nM	0.56	0.42	0.38	0.34

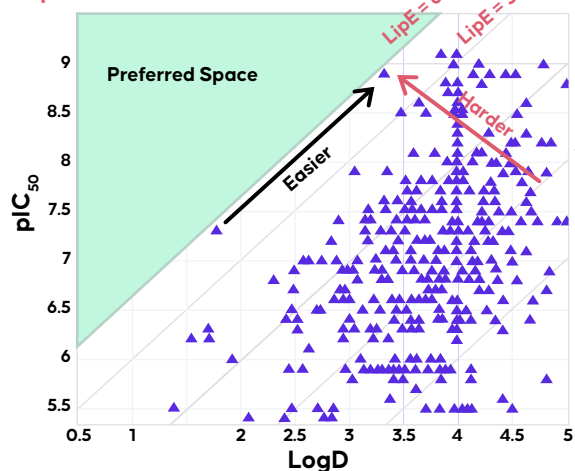
## Energy Estimates for Common Interactions

Interaction	ΔG kcal/mol	Fold potency
H-Bond	-1.4	10
Salt Bridge	-3.4	300
-Me (lipophilicity)	-0.7	3
-Cl (lipophilicity)	-1.0	5
-Ph (lipophilicity)	-2.5	60
-Me (buried)	-1.4	10
-Ph (buried) K <sub>on</sub> = 10 <sup>7</sup> M <sup>-1</sup> s <sup>-1</sup>	-3.4	300
Each rotatable bond	+0.7	3
N-S interaction	-0.7	3
Halogen bonding (Cl-O)	-1.2	9
Aromatic C-H bonding	-1.4	10
C-C bond energy	80	10 <sup>57</sup>

## Hansch Lipophilicity Constants

Group	Aromatic	Aliphatic
OH	-0.67	-1.16
CN	-0.57	-0.84
F	0.14	-0.17
OMe	0.0	-1.0
OCHF <sub>2</sub>	0.31	-0.5
Me	0.56	0.5
Cl	0.71	-0.1
CF <sub>3</sub>	0.88	0.0
OCF <sub>3</sub>	1.04	0.0
c-propyl	1.14	1.2
t-Butyl	1.98	1.98
phenyl	1.96	2.13

## LipE Plot



## Binding Kinetics

$K_i = \frac{k_{off}}{k_{on}}$	k <sub>on</sub>	Comment	Potency	Occupancy t <sub>1/2</sub> (if k <sub>on</sub> = 10 <sup>7</sup> M <sup>-1</sup> s <sup>-1</sup> )
	10 <sup>9</sup> M <sup>-1</sup> s <sup>-1</sup>	Rare: diffusion control	10 nM	7 sec
	10 <sup>7</sup> M <sup>-1</sup> s <sup>-1</sup>	Common: fast on	1 nM	70 sec
	10 <sup>5</sup> M <sup>-1</sup> s <sup>-1</sup>	Rare: rearrangement	0.1 nM	7 min
			10 pM	1.9 hour

## Bond Lengths and Distances (Å)

C-H	1.09	C-Cl	1.77	O-H	0.96
C-C	1.54	C-Br	1.94	N-H	1.01
C-N	1.47	C-I	2.14	H-H	0.74
C-O	1.43	C=O	1.2	O=O	1.21
C-S	1.82	C=C	1.34		

1 Å = 0.1 nM

Hydrogen bond: 2.7 - 3.0

π-stacking C-C: 3.3 - 4.3

Edge to face C-C: 3.7 - 4.7

## Van der Waals Radii (Å)

H	1.20	C	1.70	N	1.55	O	1.52	F	1.35
				P	1.90	S	1.85	Cl	1.80
								I	2.15

## Abbreviations

K <sub>i</sub>	Inhibition constant	nM
CL <sub>int,u</sub>	Unbound intrinsic clearance	μL/min/mg
LipE	Lipophilic efficiency	
k <sub>on</sub>	Association rate constant	M <sup>-1</sup> s <sup>-1</sup>
k <sub>off</sub>	Dissociation rate constant	s <sup>-1</sup>
LE	Ligand efficiency	
MWt	Molecular weight	g/mol
t <sub>1/2</sub>	Half-life	h

## Ionization at pH 7.4

Acid		Base	
pKa	%	pKa	%
4.4	99.9	5.4	1
5.4	99	6.4	10
6.4	90	7.4	50
7.4	50	8.4	90
8.4	10	9.4	99
9.4	1	10.4	99.9