QSAR Examples

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7-Substituted 4-Hydroxyquinoline-3-carboxylic Acids as Inhibitors of Cell Respriation

(K. J. Shah and E. A. Coats, J. Med. Chem. 20, 1001 (1977))

Substituent R	pI_{50} malate deh.	pI_{50} ascites	π	MR *)
H	-	2.98	0.00	0.103
Cl	2.44	3.84	0.71	0.603
F	1.98	3.30	0.14	0.092
OCH_3	-	3.28	-0.02	0.787
$COCH_3$	3.04	3.10	-0.55	1.118
$N(CH_3)_2$	3.32	3.33	0.18	1.555
$OCH_2C_6H_5$	4.49	4.41	1.66	3.219
$OCH_2C_6H_3(3,4\text{-}Cl_2)$	5.32	4.82	3.08	4.219
NO_2	2.72	3.24	-0.28	0.736
$CONH_2$	3.13	2.24	-1.49	0.981
COOH	2.97	2.24	-0.32	0.693
SO_2CH_3	3.18	2.75	-1.63	1.349
OH	3.31	3.04	-0.67	0.285
SO_2NH_2	3.02	2.47	-1.82	1.228

Malatdehydrogenase Inhibition

Intercorrelation π vs. MR: $r^2 = 0.50$

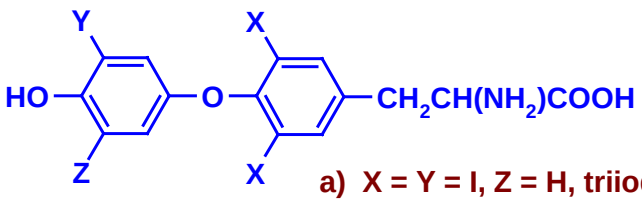
π	(n = 12; r = 0.637; s = 0.714; F = 6.82)
MR	**pI_{50} = 0.688 (±0.17) MR + 2.322 (±0.31)**
	(n = 12; r = 0.941; s = 0.314; F = 77.16)
π (n.s.), MR	(n = 12; r = 0.942; s = 0.328; F = 35.33)

Respiration Inhibition of Ascites Tumour Cells

Intercorrelation π vs. MR: $r^2 = 0.45$

π	**pI_{50} = 0.524 (±0.15) π + 3.255 (±0.18)**
	(n = 14; r = 0.914; s = 0.314; F = 60.89)
MR	(n = 14; r = 0.696; s = 0.556; F = 11.24)
π, MR (n.s.)	(n = 14; r = 0.921; s = 0.315; F = 30.73)

The Role of Iodine in the Thyroid Hormones



a) X = Y = I, Z = H, triiodothyronine, T3
b) X = Y = Z = I, thyroxine, T4

c) X = I, Y = i-propyl, Z = H
d) X = CH_3, Y = i-propyl, Z = H

log BA = 1.35 π_X + 1.34 π_Y - 1.32 [Y-size > I] - 0.36 π_Z
- 0.66 $\sigma_{Y.Z}$ - 0.89 D - 2.836
(n = 36; r = 0.938; s = 0.304)

Activity increases with increasing lipophilicity (= size) of X,
Activity increases with increasing lipophilicity (= size) of Y,
as long as Y is not larger than an iodine atom,
Activity decreases with increasing lipophilicity (= size) of Z,
Activity decreases with electron acceptors in Y and Z,
Activity decreases significantly by O-methylation;

i.e. iodine and *iso*-propyl are the "best" Y-substituents;
mid-size Y-alkyl residues should be more active than Y = iodine.

Natural Hormones:

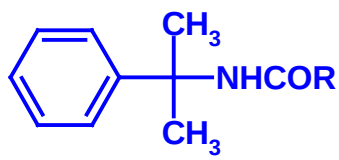
T_3, X = Y = I, Z = H	100 %	biological activity
T_4, X = Y = Z = I	18 %	biological activity

Synthetic Analogs:

X = I, Y = *iso*-propyl, Z = H	142 %	biological activity
X = Z = I, Y = *iso*-propyl	55 %	biological activity
X = Me, Y = *iso*-propyl, Z = H	3.6 %	biological activity

Optimization of a Herbicidal Lead Structure
Bromobutide – A QSAR Success Story

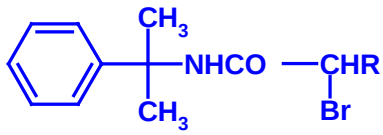
T. Fujita, in: QSAR and Strategies in the Design of Bioactive Compounds, J. K. Seydel, Hrsg., VCH, Weinheim, 1985, p. 207-218



The chemical variation of a herbicidal lead structure showed that large residues R increase biological activity if they are not too lipophilic.

$pI_{50} = - 0.15\ \pi^2 + 0.94\ \pi - 0.35\ E_s + 2.88$
$(n = 41; r = 0.933; s = 0.267)$
optimum lipophilicity $\pi_o = 3.3$

Further variation with large substituents of equal lipophilicity showed that compounds with the largest substituents had the highest activities.

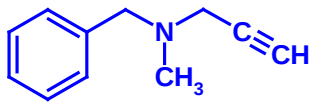


$pI_{50} = - 0.20\ E_s^2 - 1.23\ E_s + 4.393$
$(n = 14; r = 0.940; s = 0.242)$

The *tert*.-butyl analog bromobutide was selected as candidate for further development, because of high selectivity and ease of synthesis.

Monoaminoxidase Inhibitors

Y. C. Martin et al., J. Med. Chem. 18, 883 (1975)

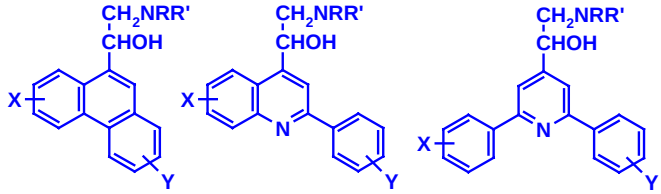


Pargyline

$pI_{50} = 0.25\ \pi - 0.35\ pK_a^2 + 4.58\ pK_a + 1.02\ D - 7.48$
$(n = 47; r = 0.876; s = 0.58)$
optimum pK_a value = 6.2

The model (D = indicator variable for ortho-substituted analogs) explains why the $-CH_2-C{\equiv}N$ analog ($pK_a = 3.5$) is a weaker MAO inhibitor than the $-CH_2-C{\equiv}CH$ analog ($pK_a = 6.5$). The pI_{50} values of six new analogs were correctly predicted by this model.

Antimalarial Activity of Substituted Phenanthrenes, Quinolines and Pyridines

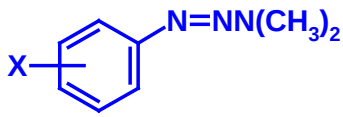


log 1/C = 0.576(±0.09) Σσ + 0.168 (±0.05) Σπ + 0.105 (±0.05) log P
- 0.167 (±0.07) log (ßP + 1) - 0.169 (±0.10) c-side
+ 0.319 (±0.136) CNR_2 - 0.139 (±0.06) AB - 0.795 (±0.06) <3-cures
+ 0.278 (±0.11) MR-4´-Q + 0.252 (±0.18) Me-6.8-Q
+ 0.084 (±0.10) 2-Pip + 0.151 (±0.19) NBrPy
- 0.683 (±0.22) Q2P378 + 0.267 (±0.11) Py + 2.726 (±0.15)

log ß = - 3.959 optimum log P = 4.19

(n = 646; r = 0.898; s = 0.309)

Antitumor Activity and Chemical Stability of Triazenes



log 1/C = 0.100 log P - 0.042 $(\log P)^2$ - 0.312 $\Sigma\sigma^+$
- 0.178 MR-2.6 + 0.391 E_s-R + 4.124

optimum log P = 1.18

(n = 61; r = 0.836; s = 0.191)

log k_X/k_H = - 4.42 σ - 0.016

(n = 14; r = 0.995; s = 0.171)

Quantum Chemical Parameters in Hansch-Analyses

Mutagenic activity of triazenes

A. J. Shusterman et al., Mol. Pharmacol. 36, 939 (1989)

$\log 1/C = 1.04\ (\pm 0.17) \log P - 1.63\ (\pm 0.35)\ \sigma^{+} + 3.06$
(n = 17; r = 0.974; s = 0.315)

$\log 1/C = 0.95\ (\pm 0.32) \log P + 1.91\ (\pm 0.89)\ \varepsilon_{HOMO} + 19.85$
(n = 17; r = 0.912; s = 0.571)

$\log 1/C = 0.92\ (\pm 0.36) \log P - 6.90\ (\pm 3.96)\ qN_{1\text{-}HOMO} + 5.70$
(n = 17; r = 0.887; s = 0.641)

All compounds, including heterocyclic analogs:

$\log 1/C = 0.95\ (\pm 0.25) \log P + 2.22\ (\pm 0.88)\ \varepsilon_{HOMO} + 22.69$
(n = 21; r = 0.919; s = 0.631)

$\log 1/C = 0.97\ (\pm 0.24) \log P - 7.76\ (\pm 2.73)\ qN_{1\text{-}HOMO} + 5.96$
(n = 21; r = 0.931; s = 0.585)

Mutagenic Activity of Nitroaromatic Compounds

R. de Compadre et al., Environ. Mol. Mutagen. 15, 44-55 (1990)

TA_{100}. TA_{98} = Revertants per nmol mutagen in two different strains of *Salmonella typhimurium*

$\log TA_{100} = 1.36\ (\pm 0.20) \log P - 1.98\ (\pm 0.39)\ \varepsilon_{LUMO} - 7.01$
(n = 47; r = 0.911; s = 0.737; F = 99.9)

$\log TA_{98} = -2.29\ (\pm 0.41)\ \varepsilon_{LUMO} + 1.62\ (\pm 0.28) \log P$
$- 4.21\ (\pm 0.80) \log (\beta P + 1) - 7.74$
optimum log P = 4.86
(n = 66; r = 0.886; s = 0.750; F = 54.3)

Mutagenic Activity of Various Nitro-substituted Aromatic Compounds, *Salmonella typhimurium* TA_{98}

A. K. Debnath et al., J. Med. Chem. 34, 786-797 (1991)

$\log TA98 = 0.65\ (\pm 0.16) \log P - 2.90\ (\pm 0.59) \log(\beta P + 1)$
$- 1.38\ (\pm 0.25)\ \varepsilon_{LUMO} + 1.88\ (\pm 0.39)\ I_1 - 2.89\ (\pm 0.81)\ I_a$
$- 4.15\ (\pm 0.58)$
$\log \beta = -5.48$ **optimum log P = 4.93**
(n = 188; r = 0.900; s = 0.886)

Transport and Distribution - Nonlinear Structure-Activity Relationships

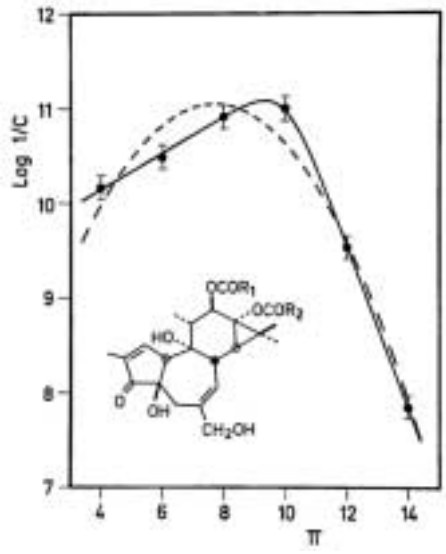
Permeation of active compounds through the skin: Inflammatory activity of phorbol esters

Compound	π	log 1/C
Phorbol-12,13-dibutyrate	4	10.17
Phorbol-12,13-dihexanoate	6	10.49
Phorbol-12,13-dioctanoate	8	10.92
Phorbol-12,13-didecanoate	10	11.00
Phorbol-12,13-didodecanoate	12	9.54
Phorbol-12,13-ditetradecanoate	14	7.85

Inflammatory Activity of Phorbol Esters

$\log 1/C = - 0.0786\ (\pm 0.042)\ \pi^2$
$+ 1.210\ (\pm 0.76)\ \pi$
$+ 6.392\ (\pm 3.12)$
optimum $\pi = 7.69$
(5.86 / 8.51)
(n = 6; r = 0.978; s = 0.320;
F = 32.39)

$\log 1/C = 0.193\ (\pm 0.041)\ \pi$
$- 1.054\ (\pm 0.093)\ \log (\beta.10^{\pi} + 1)$
$+ 9.373\ (\pm 0.30)$
$\log \beta = - 9.983$
optimum $\pi = 9.33$
(n = 6; r = 1.000; s = 0.041;
F = 1.390)



Antihistaminic Activity of Mandelic Acid Esters

Guinea pig ileum, *in vitro*; A. B. H. Funcke, M. J. E. Ernsting, R. F. Rekker and W. Th. Nauta, Arzneim.-Forsch. **3**, 503-506 (1953)

Ester	log P	log 1/C	$y_{obsd.} - y_{calc.}$ Parabolic Model	$y_{obsd.} - y_{calc.}$ Bilinear Model
Methyl	0.41	-0.52	0.31	0.09
Ethyl	0.91	-0.22	-0.05	-0.03
Propyl	1.41	0.20	-0.20	-0.04
Butyl	1.91	0.59	-0.27	-0.07
Pentyl	2.41	1.08	-0.16	0.00
Hexyl	2.91	1.52	0.00	0.04
Heptyl	3.41	1.70	-0.01	-0.14
Octyl	3.91	2.18	0.38	0.11
Nonyl	4.41	2.26	0.47	0.21
Decyl	4.91	1.45	-0.25	-0.28
Undecyl	5.41	1.28	-0.23	0.10

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Linear Model

a) first 8 compounds $\log 1/C = 0.785\ (\pm 0.06) \log P - 0.878$
$(n = 8; r = 0.997; s = 0.075; F = 1{,}158)$

b) all compounds $\log 1/C = 0.467\ (\pm 0.23) \log P - 0.310$
$(n = 11; r = 0.834; s = 0.540; F = 20.53)$

Parabolic Model

$\log 1/C = -0.189\ (\pm 0.09)\ (\log P)^2 + 1.566\ (\pm 0.56) \log P - 1.438$
$\log P_o = 4.14$ $(n = 11; r = 0.958; s = 0.298; F = 44.46)$

Franke Model

$\log 1/C = 0.802\ (\pm 0.11) \log P - 0.585\ (\pm 0.15)\ (\log [P > P_x])^2 + 0.901$
$\log P_x = 3.433$ $\log P_o = 4.12$
$(n = 11; r = 0.989; s = 0.164; F = 104.54)$

"Cut-off " Model

$\log 1/C = 0.785\ (\pm 0.08) \log P - 1.764\ (\pm 0.32) \log [P > P_o] - 0.878$
$\log P_o = 4.17$ $(n = 11; r = 0.994; s = 0.121; F = 195.13)$

Bilinear Model

$\log 1/C = 0.852\ (\pm 0.12) \log P - 2.257\ (\pm 0.55) \log (\beta P + 1) - 0.963$
$\log \beta = -4.356$ $\log P_o = 4.14$
$(n = 11; r = 0.990; s = 0.160; F = 109.96)$

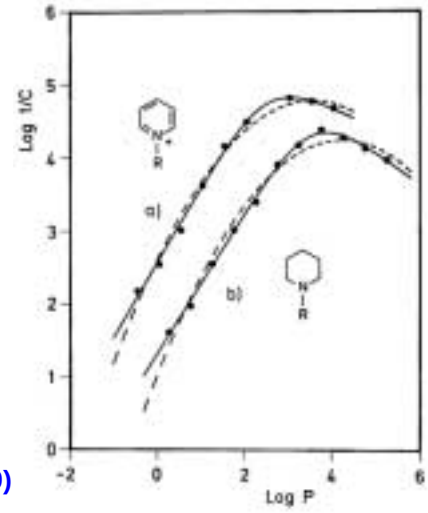
Hemolytic Activity of N-n-Alkylpyridinium Compounds and N-n-Alkylpiperidines

a) N-n-Alkylpyridinium compounds

log 1/C = 1.028 (±0.09) log P
- 1.316 (±0.24) log (ßP + 1) - 2.559
log ß = - 2.499
optimum log P = 3.05
(n = 9; r = 0.998; s = 0.071; F = 541)

b) N-n-Alkylpiperidines

log 1/C = 0.963 (±0.04) log P
- 1.406 (±0.12) log (ßP + 1) + 1.304
log ß = - 3.55
optimum log P = 3.89
(n = 11; r = 0.999; s = 0.050; F = 1,269)



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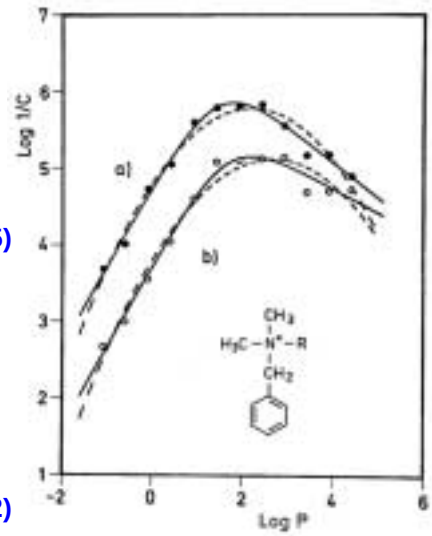
Bacteriostatic Activity of N-Benzyl,N,N-dimethyl, N-alkylammonium Compounds

a) vs. *Staphylococcus aureus*

log 1/C = 1.047 (±0.19) log P
- 1.507 (±0.19) log (ßP + 1)
+ 4.757
log ß = - 1.438
optimum log P = 1.79
(n = 12; r = 0.993; s = 0.100; F = 177.5)

a) vs. *Clostridium welchii*

log 1/C = 1.061 (±0.12) log P
- 1.37 (±0.23) log (ßP + 1)
+ 3.723
log ß = - 1.656
optimum log P = 2.18
(n = 12; r = 0.992; s = 0.125; F = 169.2)



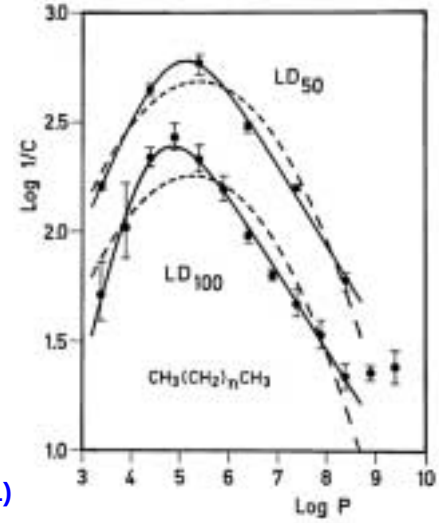
Toxicity of n-Alkanes in Mice

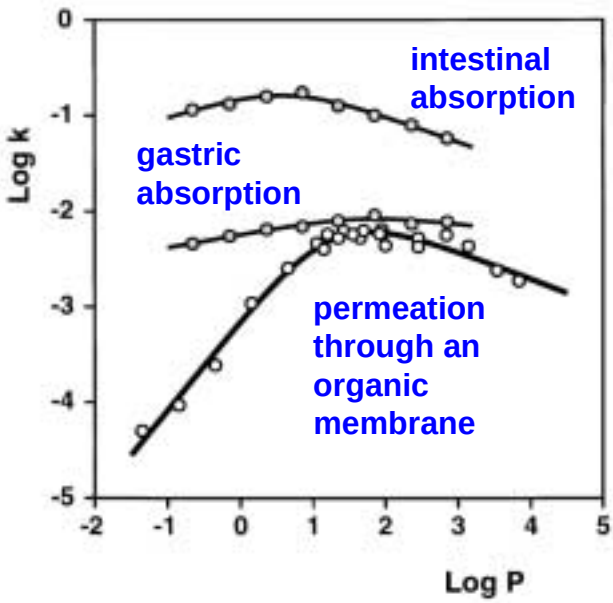
LD_{50} values

log 1/C = 0.524 (±0.16) log P
- 0.886 (±0.22) log (ßP + 1)
+ 0.443
log ß = - 4.956
optimum log P = 5.12
(n = 6; r = 0.998; s = 0.038; F = 150.4)

LD_{100} values

log 1/C = 0.956 (±0.11) log P
- 1.306 (±0.13) log (ßP + 1)
- 1.498
log ß = - 4.412
optimum log P = 4.85
(n = 11; r = 0.996; s = 0.039; F = 288.1)





Transport, Absorption and Distribution of Organic Compounds and Drugs

Barbiturates, permeation through an organic membrane

$\log k_{abs} = 0.949\ (\pm 0.06) \log P - 1.238\ (\pm 0.11) \log (\beta P + 1) - 3.131$

$\log \beta = -5.27$ optimum log P = 1.79

(n = 23; r = 0.992; s = 0.081; F = 389.66)

Homologous alkyl carbamates, gastric absorption

$\log k_{abs} = 0.138\ (\pm 0.06) \log P - 0.228\ (\pm 0.16) \log (\beta P + 1) - 2.244$

$\log \beta = -1.678$ optimum log P = 1.87

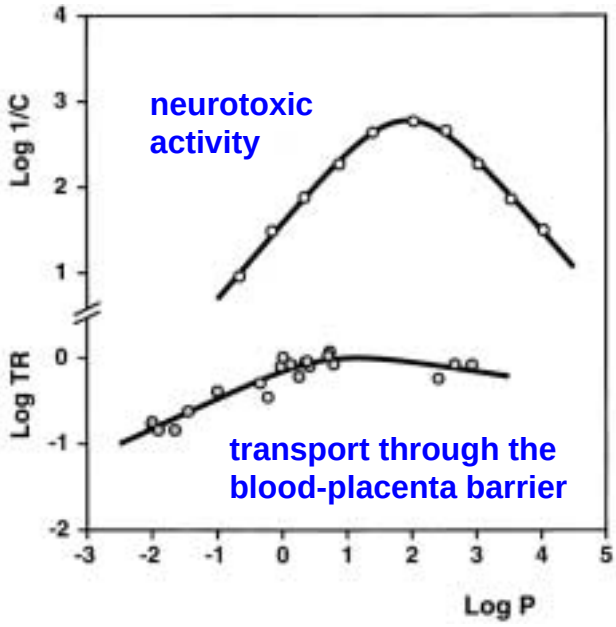
(n = 8; r = 0.971; s = 0.030; F = 22.14)

Homologous alkyl carbamates, intestinal absorption

$\log k_{abs} = 0.234\ (\pm 0.10) \log P - 0.502\ (\pm 0.15) \log (\beta P + 1) - 0.786$

$\log \beta = -0.621$ optimum log P = 0.56

(n = 8; r = 0.989; s = 0.031; F = 61.10)



Transport, Absorption and Distribution of Organic Compounds and Drugs

Alcohols, neurotoxicity, permeation of blood-brain barrier

$\log 1/C = - 0.269\ (\pm 0.038)\ (\log P)^2 + 1.030\ (\pm 0.14)\ \log P + 1.674$

optimum log P = 1.92 (1.82 / 2.02)

(n = 10; r = 0.989; s = 0.101; F = 154.9)

$\log 1/C = + 0.892\ (\pm 0.050)\ \log P - 1.766\ (\pm 0.10)\ \log (\beta P + 1) + 1.586$

log ß = -1.933 optimum log P = 1.94

(n = 10; r = 0.998; s = 0.041; F = 637.6)

Various drugs, permeation of blood-placenta barrier

$\log TR = 0.354\ (\pm 0.06)\ \log P - 0.469\ (\pm 0.13)\ \log (\beta P + 1) - 0.116$

log ß = - 0.658 optimum log P = 1.15

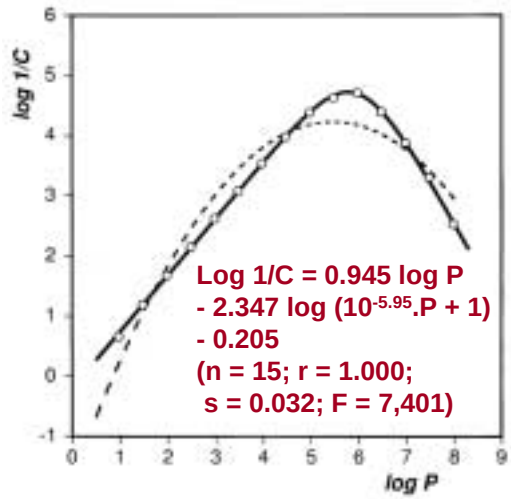
(n = 21; r = 0.949; s = 0.106; F = 51.17)

Antibacterial Activity of Homologous Aliphatic Amines vs. *Rhinocladium beurmanni*

(E. J. Lien and P. H. Wang, *J. Pharm. Sci.* 69, 648-650 (1980))

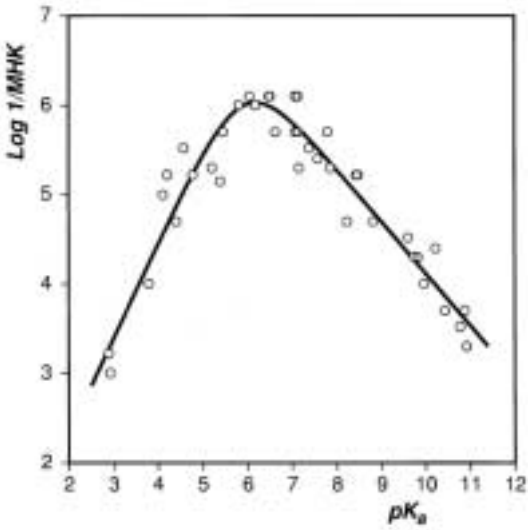
Parabolic Model, log P
r = 0.967;
s = 0.354;
F = 85.61

Parabolic Model and log MW term
r = 0.995;
s = 0.148;
F = 345.1



Antibacterial Activity of Sulfonamides vs. *E. coli*

C. Silipo and A. Vittoria, Farmaco. Ed. Sci. 34, 858-868 (1979)



$$\log 1/C = 1.044\ (\pm 0.13)\ pK_a - 1.640\ (\pm 0.18)\ \log (\beta . 10^{pK_a} + 1) + 0.275\ (\pm 0.65)$$

$\log \beta = -5.96$

optimum $pK_a = 6.22$

(n = 39; r = 0.956; s = 0.275; F = 124.1)

Inhibition of Monoaminoxidase by Amines and Alcohols at Different pH Values

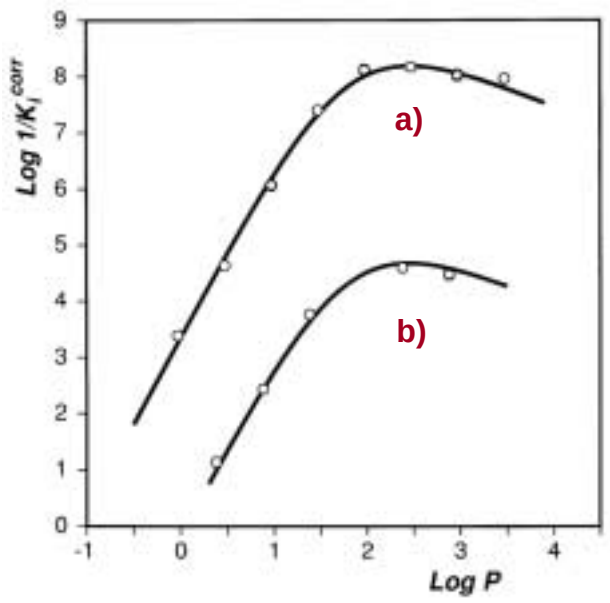
C. M. McEwen et al., J. Biol. Chem. 243, 5217-5225 (1968)
H. Kubinyi, Prog. Drug Res. 23, 97-108 (1979)

Compound	log P	pH	K_i, mM	log $1/K_i$	log $1/K_i^{corr}$
n-Propanol	0.38	8.72	72	1.14	
n-Butanol	0.88[a)]	7.51	3.6	2.44	
		8.72	3.6	2.44	
n-Pentanol	1.38	8.72	0.17	3.77	= log $1/K_i$
n-Heptanol	2.38	8.72	0.025	4.60	
n-Octanol	2.88	7.51	0.034	4.47	
		8.72	0.032	4.49	

[a)] experimental value, all other values extrapolated

Compound	log P	pH	K_i, mM	log $1/K_i$	log $1/K_i^{corr}$ b)
n-Propylamine	0.47	7.62	25	1.60	4.64
		8.72	2.0	2.70	4.64
n-Butylamine	0.97a)	7.51	1.2	2.92	6.07
		8.11	0.31	3.51	6.06
		8.72	0.073	4.14	6.08
n-Pentylamine	1.47	7.62	0.044	4.36	7.40
		8.72	0.0035	5.46	7.40
n-Hexylamine	1.97	7.57	0.0092	5.04	8.13
		8.72	0.00068	6.17	8.11
n-Heptylamine	2.47	7.62	0.0075	5.12	8.17
n-Octylamine	2.97	7.48	0.015	4.82	8.00
		7.62	0.010	5.00	8.04
n-Nonylamine	3.47	8.72	0.00096	6.02	7.96

a) experimental value, all other values extrapolated
b) $\log 1/K_i^{korr} = \log 1/K_i + \log (1 + 10^{pKa-pH})$; pK_a (amines) = 10.66



MAO Inhibition

a) Amines

b) Alcohols

Parabolic Model

$\log 1/K_i^{corr} = \log 1/K_i + \log (1 + 10^{pKa-pH}) =$

$- 0.717\ (\pm 0.10)\ (\log P)^2 + 3.781\ (\pm 0.35)\ \log P$

$- 3.556\ (\pm 0.18)\ I + 3.242\ (\pm 0.26)$

optimum log P = 2.64

(n = 21; r = 0.997; s = 0.185; F = 937)

Bilinear Model

$\log 1/K_i^{corr} = \log 1/K_i + \log (1 + 10^{pKa-pH}) =$

$3.130\ (\pm 0.17)\ \log P - 3.797\ (\pm 0.32)\ \log (\beta P + 1)$

$- 3.507\ (\pm 0.12)\ I + 3.379\ (\pm 0.15)$

$\log \beta = - 1.781$ optimum log P = 2.45

(n = 21; r = 0.999; s = 0.118; F = 1,737)

Hugo Kubinyi, www.kubinyi.de

Absorption of Acids and Phenols from the Rat Colon, *in situ*, at pH = 6.8

Compound	log P	pK_a	log %ABS
5-Nitrosalicylic acid	1.98	2.3	0.30
m-Nitrobenzoic acid	1.83	3.4	1.00
Salicylic acid	2.26	3.0	1.08
Benzoic acid	1.85	4.2	1.28
Phenylbutazone	3.22	4.4	1.58
o-Nitrophenol	1.79	7.0	1.74
Thiopental	2.50	7.6	1.70
p-Hydroxypropio-phenone	1.85	7.8	1.66
m-Nitrophenol	2.00	8.2	1.64
Phenol	1.46	9.9	1.55

Lien. E. J., in Drug Design. Volume V, Ariëns, E. J., Ed., Academic Press, New York, 1975, p. 81–132

$$\log \% ABS = 0.156\ (\pm 0.08)\ (pK_a - pH) + 0.366\ (\pm 0.44)\ \log P + 0.755$$
$$(n = 10;\ r = 0.866;\ s = 0.258)$$

Two wrong assumptions: log % ABS and pK_a - pH !!

Compound	log P	pK_a	pK_a - pH	log P_{app}	log k_{abs}
5-Nitrosalicylic acid	1.98	2.3	-4.5	-2.52	-1.69
m-Nitrobenzoic acid	1.83	3.4	-3.4	-1.57	-0.98
Salicylic acid	2.26	3.0	-3.8	-1.54	-0.89
Benzoic acid	1.85	4.2	-2.6	-0.75	-0.68
Phenylbutazone	3.22	4.4	-2.4	0.82	-0.32
o-Nitrophenol	1.79	7.0	0.2	1.58	-0.10
Thiopental	2.50	7.6	0.8	2.44	-0.16
p-Hydroxypropio-phenone	1.85	7.8	1.0	1.81	-0.21
m-Nitrophenol	2.00	8.2	1.4	2.00	-0.24
Phenol	1.46	9.9	3.1	1.46	-0.35

Hugo Kubinyi, www.kubinyi.de

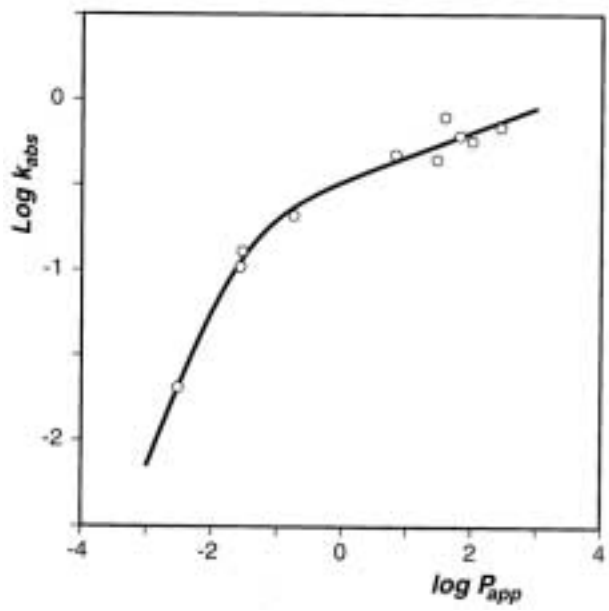
R. A. Scherrer and S. M. Howard, J. Med. Chem. 20, 53-58 (1977)

$$\log \% ABS = -0.079\ (\log P_{app})^2 + 0.236\ \log P_{app} + 1.503$$
$$\text{optimum } \log P_{app} = 1.49$$
$$(n = 10;\ r = 0.982;\ s = 0.096)$$

$$\log k_{abs} = -0.078\ (\pm 0.041)\ (\log P_{app})^2 + 0.265\ (\pm 0.045)\ \log P_{app} - 0.425$$
$$\text{optimum } \log P_{app} = 1.70$$
$$(n = 10;\ r = 0.984;\ s = 0.102;\ F = 105.87)$$

H. Kubinyi, Arzneim.-Forsch. (Drug Res.) 29, 1067-1080 (1979)

$$\log k_{abs} = 1.024\ (\pm 0.31)\ \log P_{app} - 0.881\ (\pm 0.36)\ \log (\beta P_{app} + 1) + 0.935$$
$$\log \beta = 1.600$$
$$(n = 10;\ r = 0.991;\ s = 0.081;\ F = 112.86)$$



Absorption from the Rat Colon, *in situ*, at pH = 6.8

(bilinear model)