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QSAR and ADME

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Abstract—The prediction from structure of ADME (absorption, distribution, metabolism, elimination) of drug candidates is an important goal to achieve since it can considerably reduce the cost of drug development. Using our database of 10,700 QSAR, we are now reaching the point where we can make many useful comparisons that illustrate how ADME is a practical way to describe the way organic compounds react with living systems. We also show that Caco-2 cells are useful to model absorption, but the most generally useful parameter is the octanol/water partition coefficient. It should be noted, however, that in our opinion, an in silico prediction of ADME is still a long way in the future.

1. Introduction

The latest buzzword in drug development is ADME (absorption, distribution, metabolism, elimination). Except for metabolism, it is possible to make some useful predictions from structure that can guide early drug development. To obtain some understanding how enormously complex this problem is, one needs a large database of QSAR from as many diverse studies as possible. At the present time our group has some 18,800 QSAR, of which 10,700 are from biological systems. These range in complexity from DNA to enzymes, organelles, membranes, organs and whole animals including humans. About 8800 of the equations are from physical organic chemistry for comparative, mechanistic purposes. In this report, we are considering reports measuring the permeability of drugs and other organic compounds into Caco-2 cells, which are models for the intestinal lining. This is not a simple problem because in essence, one wants to know about the levels reached in many parts of whole animals. The subject has been recently reviewed by Waterbeemd and Gifford[1] and Bergström et al.[2] to suggest an algorithm for general use. In this report we are interested in the use of parameters that we have been developing for the past 40 years to characterize the properties that determine the interaction of organic chemicals with living systems or their parts. The most generally useful parameter is the octanol/water partition coefficient. More than half (5522) of the QSAR in our bio QSAR database contains such a term, often accompanied by parameters modeling electronic and/or size effects. Terms for polarizability[3] (CMR or NVE) occur in 2576 equations and steric parameters (B1, B5, Es)[4] occur in 1974 examples. We have used ClogP and CMR programs from the BioByte Corporation.[5]

2. Results

First we consider work done with Caco-2 cells to assess drug absorption via the intestines. At present, we have 29 QSAR using data reported on such cells. Of these, 26 contain Clog P terms. Two are based on Pi, the hydrophobic parameter derived for substituents. Of these 26, 9 are simple QSAR with single linear log P terms as the only parameter. Ten contain a single log P term plus an additional negative term: MgVol or CMR. Thus we can see a close relationship between penetration of Caco-2 cell membranes and hydrophobic properties. Seven of the QSAR are based on nonlinear hydrophobic terms.

The best published result comes from Hopfinger et al.'s laboratory.[7] From their data, we have formulated QSAR 1 (Table 1):

$$\log kP = 0.41(\pm 0.06)\,\mathrm{Clog}P - 0.06(\pm 0.02)\,\mathrm{Clog}P^2 - 0.31(\pm 0.16)\mathrm{MgVol} + 1.43(\pm 0.31) \quad (1)$$

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Table 1. Results with QSAR 1

		log *kP*	Y Pred	Dev	Clog *P*	MgVol
1	Diazepam	1.52	1.45	0.07	2.96	2.07
2	Caffeine	1.49	0.98	0.51	−0.04	1.36
3	Phenytoin	1.43	1.43	0.00	2.09	1.87
4	Alprenolol	1.40	1.41	0.00	2.65	2.16
5	Testosterone	1.40	1.37	0.03	3.41	2.38
6	Phencyclidine	1.39	1.25	0.14	5.10	2.15
7	Desipramine	1.38	1.33	0.06	4.47	2.26
8	Metoprolol	1.37	1.19	0.18	1.49	2.26
9	Progesterone	1.37	1.27	0.11	3.97	2.62
10	Salicyclic acid	1.34	1.72	−0.38	2.19	0.99
11	Clonidine	1.39	1.41	−0.02	1.43	1.53
12	Corticosterone	1.33	1.21	0.11	2.51	2.74
13	Indomethacin	1.31	1.28	0.03	4.18	2.53
14	Chlorpromazine	1.30	1.13	0.17	5.30	2.41
15	Nicotine	1.29	1.31	−0.02	0.88	1.37
16	Estradiol	1.23	1.41	−0.18	3.78	2.20
17	Pindolol	1.22	1.31	−0.09	1.67	2.01
18	Hydrocortisone	1.15	1.11	0.04	1.89	2.80
19	Timolol	1.11	1.09	0.02	1.21	2.38
20	Dexamethasone	1.09	1.05	0.04	1.79	2.91
21	Scopolamine	1.07	0.84	0.23	0.29	2.23
22	Dopamine	0.97	1.11	−0.14	0.17	1.22
23	Labetalol	0.97	1.24	−0.27	2.50	2.64
24	Bremazocine	0.90	1.29	−0.39	3.82	2.58
25	Nadolol	0.59	0.79	−0.20	0.38	2.49
26*	Atenolol	−0.28	0.70	−0.98	−0.11	2.18
27*	Terbutaline	−0.33	1.03	−1.36	0.48	1.84
28	Ganciclovir	−0.42	−0.54	0.12	−2.54	1.72
29*	Sulfasalazine	−0.52	1.25	−1.77	3.88	2.70
30	Acyclovir	−0.60	−0.40	−0.21	−2.42	1.52
31	Aminopyrine	1.56	1.20	0.36	1.04	1.87
32	Propranolol	1.34	1.42	−0.08	2.75	2.15
33	Warfarin	1.32	1.38	−0.05	2.90	2.31
34	Meloxicam	1.29	1.32	−0.03	2.29	2.32
35	Zidovudine	0.84	0.87	−0.03	0.04	1.82
36	Urea	0.66	0.44	0.22	−1.66	0.46
37*	Sucrose	0.23	−1.11	1.34	−3.09	2.23
38	Mannitol	−0.42	−0.07	−0.35	−2.05	1.31

*Outliers.

$n = 34$, $r^2 = 0.870$, $s = 0.205$, $q^2 = 0.820$, optimum Clog $P = 3.35$, outliers: atenolol terbutaline, sulfasalazine, sucrose.

In the above QSAR, *kP* is the rate of permeability and MgVol is the molecular volume of the molecule. Its negative coefficient shows that size of the molecule can have a role to play in penetration. Hopfinger's group obtained a QSAR of similar quality using different parameters that do not allow us to make comparisons with our studies on membrane penetration.

Turning now to other examples from the literature where it was possible to establish optimum values for log *P* for penetration is Caco2 cells, we find four examples. QSAR 2 was derived from data of Bravi and Wikel[8] for miscellaneous drugs (Table 2):

$$\begin{aligned}\text{logPerm} = {} & 1.35(\pm 0.36)\text{Clog}P \\ & - 2.90(\pm 0.82)\text{bilin Clog}P \\ & - 0.62(\pm 0.58)\text{I-COOH} + 6.73(\pm 0.55) \quad (2)\end{aligned}$$

$n = 15$, $r^2 = 0.905$, $s = 0.376$, $q^2 = 0.782$, optimum Clog $P = 2.40$.

Perm = permeability factor. The indicator variable I-COOH is assigned the value of 1 for compounds containing a carboxylic acid moiety. Clog *P* calculates the neutral value for such acids. The bilinear term[8] in QSAR indicates that activity first increases linearly up to an inflection point and then decreases linearly, in contrast to the symmetrical curve of where log P^2 describes a parabola.

Data from Tantishaiyakul[9] *for miscellaneous drugs* (Table 3):

$$\begin{aligned}\text{logPerm} = {} & 0.54(\pm 0.08)\text{Clog}P \\ & - 0.55(\pm 0.11)\text{bilin C log}P - 5.09 \quad (3)\end{aligned}$$

$n = 39$, $r^2 = 0.880$, $s = 0.200$, $q^2 = 0.859$, optimum Clog $P = 2.35$, outliers: sucrose, urea, sulfastalazine, chlorothiazole, pirenzepine, terbutaline, ranitidine,

Table 2. Results with QSAR 2

		logPerm	Y Pred Perm	Dev	Clog *P*	I-COOH
1	Corticosterone	−4.26	−4.27	0.01	2.32	0.00
2	Testosterone	−4.29	−4.77	0.48	3.22	0.00
3	Propanol	−4.38	−4.36	0.01	2.75	0.00
4	Alprenolol	−4.39	−4.31	−0.08	2.65	0.00
5	Warfarin	−4.42	−4.46	0.05	2.90	0.00
6	Metoprolol	−4.57	−5.00	0.43	1.35	0.00
7*	Felodipine	−4.64	−15.34	10.69	5.58	0.00
8	Hydrocortisone	−4.67	−4.63	−0.04	1.70	0.00
9	Dexamethasone	−4.90	−4.55	−0.35	1.79	0.00
10	Salicylic acid	−4.92	−4.92	−0.01	2.19	1.00
11	Acetylsalicylic acid	−5.62	−6.00	0.38	1.02	1.00
12	Practolol	−6.05	−5.73	−0.32	0.75	0.00
13	Terbutaline	−6.42	−6.09	−0.33	0.48	0.00
14	Atenolol	−6.70	−6.88	0.18	−0.11	0.00
15*	Mannitol	−6.75	−15.42	8.68	−2.05	0.00
16	Sulfasalazine	−6.89	−6.25	−0.64	3.88	1.00
17	Olsalazine	−6.96	−7.22	0.26	4.54	1.00

*Outliers.

Table 3. Results with QSAR 3

		logPerm	Log Perm Pred	Dev	C log *P*
1*	Acebutalol	−6.29	−5.11	−1.18	1.71
2	Acetylsalicylic acid	−5.04	−4.77	−0.27	1.02
3	Acylovir	−6.60	−6.39	−0.21	−2.42
4	Alprenolol	−4.60	−4.68	0.08	2.65
5	Aminopyrine	−4.44	−4.89	0.45	0.57
6*	Atenolol	−6.28	−5.20	−1.08	−0.11
7	Bremazocine	−5.10	−4.70	−0.40	3.82
8*	Caffeine	−4.51	−5.13	0.62	−0.04
9*	Chlorothiazole	−6.72	−5.40	−1.32	−0.29
10	Chlorpromazine	−4.70	−4.73	0.03	−5.80
11*	Cimetidine	−5.86	−5.09	−0.77	0.35
12	Clonidine	−4.66	−4.71	0.05	1.43
13	Corticosterone	−4.67	−4.68	0.01	2.32
14	Desipramine	−4.61	−4.71	0.10	4.47
15	Dexamethasone	−4.91	−4.69	−0.22	1.79
16	Diazepam	−4.48	−4.69	0.21	3.17
17	Dopamine	−5.03	−5.04	0.01	0.17
18	Estradiol	−4.77	−4.70	−0.07	3.78
19	Ganciclovir	−6.42	−6.45	0.03	−2.54
20	Griseofulvin	−4.44	−4.69	0.25	1.91
21*	Hydrochlorthiazide	−6.29	−5.48	−0.81	−0.36
22	Hydrocortisone	−4.85	−4.69	−0.16	1.70
23	Indomethacin	−4.69	−4.70	0.01	4.18
24	Labetalol	−5.03	−4.68	−0.35	2.50
25	Mannitol	−6.42	−6.18	−0.24	−2.05
26	Meloxicam	−4.71	−4.68	−0.03	2.29
27	Methyl scopolamine	−6.16	−6.41	0.25	−2.47
28	Metoprolol	−4.63	−4.71	0.08	1.49
29	Nadolol	−5.41	−4.96	−0.45	0.38
30	Nevirapine	−4.52	−4.68	0.16	2.42
31	Nicotine	−4.71	−4.80	0.09	0.88
32	Phenycylidine	−4.61	−4.72	−0.11	5.10
33	Phenytoin	−4.57	−4.68	0.24	2.09
34	Pindolol	−4.78	−4.69	0.07	1.67
35*	Pirenzepine	−6.36	−5.09	0.02	0.16
36	Piroxicam	−4.45	−4.69	−1.22	1.89
37	Progesterone	−4.63	−4.70	0.02	3.78
38	Propranolol	−4.66	−4.68	0.06	2.75
39*	Ranitidine	−6.31	−5.09	2.68	0.63
40	Salicylic acid	−4.66	−4.68	−1.38	2.19
41	Scopolamine	−4.93	−4.99	−0.07	0.29
42*	Sucrose	−5.77	−8.45	−1.24	−3.09
43*	Sulfasalazine	−6.52	−5.14	0.09	3.88
44	Telmisartan	−4.82	−4.75	−0.19	7.46
45*	Terbutaline	−6.33	−5.09	−0.28	0.48
46	Testosterone	−4.60	−4.69	1.55	3.22
47	Timolol	−4.89	−4.70	0.00	1.58
48	Uracil	−5.37	−5.65	−1.06	−1.06
49*	Urea	−5.34	−6.89	−1.66	−1.66
50	Warfarin	−4.68	−4.68	2.90	2.90
51	Zidovudine	−5.16	−5.10	0.04	0.04

*Outliers.

acebutalol, hydrochlorothiazide, cimetidine, caffeine, atenolol.

This is not a very good correlation because of the number of outliers. However, optimum Clog *P* is essentially the same as for QSAR 3.

Data from Bergstrom et al.[10] *for miscellaneous drugs* (Table 4):

$$\log k = 0.57(\pm 0.11)\,\mathrm{C}\log P - 1.01(\pm 0.58)\mathrm{bilin}\,\mathrm{C}\log P - 0.11(\pm 0.06)\mathrm{CMR} + 1.53(\pm 0.64) \quad (4)$$

$n = 19$, $r^2 = 0.931$, $s = 0.368$, $q^2 = 0.871$, optimum Clog $P = 3.80$, outliers: amiloride, methotrexate, tamoxifen, theophylline.

Perm = permeability rate. The optimum Clog *P* for QSAR 4 is significantly higher than for QSAR 3, and in this respect it is more like QSAR 1.

Data from Yamashita et al.[11] *for miscellaneous chemicals and drugs* (Table 5):

$$\log k\mathrm{Perm} = 0.65(\pm 0.19)\,\mathrm{C}\log P - 0.85(\pm 0.37)\mathrm{bilin}\,\mathrm{C}\log P - 0.12(\pm 0.04)\mathrm{CMR} - 4.75(\pm 0.41) \quad (5)$$

$n = 21$, $r^2 = 0.837$, $s = 0.329$, $q^2 = 0.620$, optimum Clog $P = 2.83$, outliers: acyclovir, caffeine, fluconazole, naloxone, trovafloxacin.

Perm = apparent permeability rate. The CMR (calculated polarizability) term can be ambivalent in that it does contain volume and polarizability components present in the Lorentz–Lorenz equation: $\mathrm{MR} = n^2 - 1/n^2 + 2(\mathrm{MW}/d)$; where n = refractive index, d = density and MW = molecular weight.

It is of interest that QSAR 2-5 are all bilinear equations. That is, activity first increases linearly and then decreases linearly. This is in contrast to QSAR where we find a parabolic relationship. The optimum values are 3.35, 2.40, 2.35, 3.80 and 2.80—giving an average value at 2.94. Thus, we see that log *P* is a most significant parameter in describing Caco-2 absorption of drugs. In fact, since it can be calculated rapidly, it is a time-saving approach to study absorption compared to measurements of penetration rate using Caco-2 cells.

2.1. Intestinal adsorption

For a drug administered orally, the first step is intestinal absorption. This process can be compared with the QSAR for the penetration of Caco-2 cells (QSAR 1-5).

Data from Bermjo et al.[12] *Rate of absorption by small intestine of male wister rat* (Table 6):

$$\log k = 0.44(\pm 0.04)\log P - 0.47(\pm 0.08)\mathrm{bilin}\log P + 0.30(\pm 0.03) \quad (6)$$

$n = 16$, $r^2 = 0.988$, $s = 0.045$, $q^2 = 0.984$, optimum log $P = 2.44$. log *P* values were experimentally determined.

Table 4. Results with QSAR 4

		log *k*	Y Pred	Dev	Clog *P*	CMR
1	Acyclovir	−0.92	−0.45	−0.47	−2.42	5.45
2*	Amiloride	−0.49	0.89	−1.39	0.11	5.39
3	Amitryptyline	2.10	2.09	0.01	4.85	9.15
4	Amoxacillin	−0.74	−0.56	−0.18	−1.87	9.3
5	Atropine	1.29	1.38	−0.09	1.30	8.15
6	Chlorpromazine	1.86	1.88	−0.02	5.30	9.38
7	Ciprofloxacin	0.88	0.16	0.73	−0.73	8.72
8	Desipramine	2.01	2.28	−0.28	4.47	8.54
9	Doxycyline	0.35	0.02	0.33	−0.50	11.29
10	Ergonovine	0.83	1.20	−0.36	1.23	9.37
11	Erythromycin	0.05	0.35	−0.30	1.61	18.93
12	Ethinyl estradiol	2.58	2.39	0.19	3.86	8.65
13	Folinic acid	−1.52	−1.61	0.09	−3.22	11.86
14	Indomethacine	2.04	2.25	−0.21	4.18	9.51
15*	Methothrexate	−1.52	−0.59	−0.93	−0.53	11.64
16	Phenazopyridine	2.45	1.95	0.51	2.05	6.74
17	Primaquine	2.25	2.11	0.13	2.60	7.84
18	Promethazine	2.22	2.26	−0.04	4.40	8.89
19*	Tamoxifen	—	−2.79	—	6.82	12.07
20*	Theophylline	1.83	0.98	0.84	−0.03	4.53
21	Verapamil	2.19	1.77	0.42	4.47	13.15
22	Warfarin	1.77	2.16	−0.39	2.9	8.72
23	Zidovudine	0.79	0.86	−0.07	0.04	6.36

*Outliers.

Table 5. Results with QSAR 5

		log *kP*	Y Pred	Dev	CMR	Clog *P*
1	Acetylsalicylic acid	−4.51	−4.61	0.10	4.46	1.02
2*	Acyclovir	−5.70	−9.01	3.31	5.45	−2.42
3	Azithromycin	−5.98	−5.72	−0.26	19.73	2.64
4*	Caffeine	−4.30	−5.38	1.08	4.99	−0.04
5	Chloramphenicol	−4.69	−4.78	0.09	7..31	1.28
6	Cimetidine	−5.51	−5.30	−0.21	6.90	0.38
7	Clonidine	−4.52	−4.53	0.01	5.81	1.43
8	Desipramine	−4.67	−4.66	−0.01	8.54	4.47
9	Dexamethasone	−4.63	−4.84	0.21	10.07	1.79
10	Diazepam	−4.15	−4.38	0.23	8.12	2.96
11	Doxorubicin	−6.80	−6.08	−0.72	13.33	0.32
12	Erythromycin	−5.43	−5.94	0.51	18.93	1.61
13*	Fluconazole	−4.53	−6.25	1.72	7.30	−0.44
14	Ibuprofen	−4.28	−4.23	−0.05	6.12	3.68
15	Imipramine	−4.85	−4.82	−0.03	9.01	5.04
16	Mannitol	−6.19	−6.52	0.33	3.88	−2.05
17*	Naloxone	−4.55	−5.78	1.23	8.68	0.16
18	Prazocin	−4.36	−4.75	0.39	10.20	2.03
19	Propranolol	−4.56	−4.34	−0.22	7.83	2.75
20	Quinidine	−4.69	−4.53	−0.16	9.48	2.79
21	Sumatriptan	−5.52	−5.21	−0.31	8.20	0.74
22	Tenidap	−4.29	−4.45	0.16	8.27	2.30
23	Testosterone	−4.14	−4.44	0.30	8.27	3.41
24*	Trovafloxacin	−4.52	−6.17	1.65	10.04	−0.18
25	Valproic acid	−4.32	−3.91	−0.41	4.08	2.76
26	Ziprasidone	−4.91	−4.94	0.03	11.47	4.21

*Outliers.

Intestinal absorption of miscellaneous drugs by human intestine. Data from Norinder and Osterberg[13] (Table 7):

$$\log A = 0.79(\pm 0.18)\,\mathrm{C}\log P - 2.86(\pm 0.70)\mathrm{bilin}\,\mathrm{C}\log P + 1.12(\pm 0.41) \quad (7)$$

$n = 18$, $r^2 = 0.876$, $s = 0.707$, $q^2 = 0.752$, optimum $\log P = 2.00$, outliers: metolazone, sulpride.

The agreement in optimum $\log P$ is good between QSAR 6 and 7 and they are in line with some of the results with Caco-2 cells. There is no reason to expect quantitative

Table 6. Results with QSAR 6

	X	Y	log *k*	Y Pred	Dev	Mlog *P*
1	C_2H_5	H	−0.38	−0.38	0.00	−1.55
2	C_2H_5	*n*-Methyl	0.28	0.40	−0.12	0.27
3	C_2H_5	*n*-Ethyl	0.44	0.43	0.01	0.37
4	C_2H_5	*n*-Propyl	0.61	0.65	−0.04	1.05
5	C_2H_5	*n*-Butyl	0.75	0.74	0.01	1.48
6	C_2H_5	*n*-Pentyl	0.76	0.78	−0.02	2.11
7	C_2H_5	*n*-Hexyl	0.78	0.78	0.00	2.71
8	C_2H_5	*n*-Heptyl	0.78	0.77	0.01	3.22
9	Cy-C_3H_5	H	−0.20	−0.20	0.00	−1.12
10	Cy-C_3H_5	*n*-Methyl	0.41	0.35	0.06	0.15
11	Cy-C_3H_5	*n*-Ethyl	0.55	0.49	0.06	0.53
12	Cy-C_3H_5	*n*-Propyl	0.68	0.66	0.02	1.07
13	Cy-C_3H_5	*n*-Butyl	0.76	0.74	0.02	1.55
14	Cy-C_3H_5	*n*-Pentyl	0.78	0.78	0.00	2.06
15	Cy-C_3H_5	*n*-Hexyl	0.78	0.78	0.00	2.56
16	Cy-C_3H_5	*n*-Heptyl	0.78	0.78	0.00	3.02

Table 7. Results with QSAR 7

		log A	Y Pred	Dev	Clog *P*
1	Atenolol	0.13	1.03	−0.90	−0.11
2	Ciprofloxacin	0.66	0.54	0.12	−0.73
3	Foscarnet	−1.24	−0.60	−0.64	−2.17
4	Mannitol	−0.85	−0.50	−0.35	−2.05
5	Nordiazepam	2.29	1.51	0.78	3.02
6	Olsalazine	−2.17	−2.65	0.48	5.17
7	Oxazepam	2.11	2.23	−0.12	2.31
8	Oxprenolol	2.11	2.29	−0.18	2.09
9	Phenazone	2.11	1.27	0.84	0.20
10	Practolol	1.95	1.69	0.26	0.75
11	Raffinose	−2.37	−3.09	0.72	−5.32
12	Sulfasalazine	−1.49	−0.03	−1.46	3.88
13	Tranexamic acid	0.17	−0.31	0.48	−1.80
14	Alprenolol	2.02	1.97	0.05	2.65
15	Diazepam	2.11	1.59	0.52	2.96
16	Lactulose	−2.33	−1.72	−0.61	−3.59
17*	Metolazone	0.48	−3.13	3.61	2.06
18	Metoprolol	2.64	2.15	0.49	1.49
19	Pindolol	1.73	2.23	−0.50	1.67
20*	Sulpride	−0.48	−1.18	0.70	1.11

*Outliers.

Table 8. Results with QSAR 8

		log *k*	Y Pred	Dev	Mlog *P*	Bilin
1	Aniline	0.75	0.73	0.02	0.90	0.00
2	2-Methylaniline	0.78	0.79	−0.01	1.32	0.01
3	4-Methylaniline	0.81	0.80	0.01	1.39	0.01
4	2,4-Dimethylaniline	0.80	0.84	−0.04	1.68	0.02
5	4-Ethylaniline	0.87	0.87	0.00	1.96	0.04
6*	4-Isopropylaniline	0.81	−0.07	0.88	2.23	2.23
7	1-Naphthylamine	0.92	0.89	0.02	2.25	0.08
8	2-Naphthylamine	0.92	0.90	0.02	2.28	0.08
9	4-Propylaniline	0.90	0.90	0.00	2.40	0.10
10	4-Aminobiphenol	0.89	0.90	−0.01	2.86	0.25
11*	4-Terbutylaniline	0.83	−0.21	1.04	2.70	2.70
12*	4-Betylaniline	0.82	−0.32	1.13	3.05	3.05
13	4-Cyclohexylaniline	0.79	0.79	0.00	3.65	0.77

*Outliers.

agreement. Qualitative agreement is all one can reasonably expect.

Absorption of miscellaneous aromatic amines by rat small intestine. Data from Martin–Willadre[14] (Table 8):

$$\log k = 0.14(\pm 0.05)\log P - 0.45(\pm 0.16)\text{bilin}\log P + 0.61(\pm 0.07) \quad (8)$$

$n = 10$, $r^2 = 0.910$, $s = 0.023$, $q^2 = 0.815$, optimum $\log P = 2.6$, outliers: 4-isopropylamine, 4-tertbutylaniline, 4-betylaniline.

k is the absorption rate. Thus, we find rather good agreement in three examples for the dominant role of hydrophobicity in determining the rate of intestinal absorption. All have similar optimum values, despite being compounds of quite varied structure. While penetration rates into Caco-2 cells can still be used to model the absorption process, it would be much more economical in time and money to use Clog P values.

2.2. Drug distribution

Drug distribution is a more difficult process to characterize. There are many different compartments in the body so that it is hard to generalize from the analysis of a single site. Some time ago, we elected to consider drugs acting on the central nervous system, since a wide variety of compounds have been studied for CNS effects. A considerable number of QSAR studies indicate that there is an optimal hydrophobicity for CNS agents. In these studies, it was generally assumed that the measured CNS depression is directly proportional to the concentration in the brain. A very important conclusion from these studies is that the optimum $\log P$ was 2 ± 0.05 for 114 drugs of very widely different structures.[6] The range of optimal value is influenced by permutation and by receptor affinity. The best study we have on distribution is that from Nestorov et al.[13] These authors showed by a plot of their data against $\log P$ that a good relationship could be found for 5-*N*-alkyl-5-ethyl-barbituc acids interacting in rats after intravenous injection. $\log K$ is the tissue/plasma ratio.

Rat lung tissue[13] (Table 9):

$$\log K = 0.63(\pm 0.17)\,\text{C}\log P - 0.55(\pm 0.45) \quad (9)$$

$n = 9$, $r^2 = 0.914$, $s = 0.298$, $q^2 = 0.843$.

Rat liver tissue[13] (Table 10):

$$\log K = 0.44(\pm 0.15)\,\text{C}\log P + 0.11(\pm 0.40) \quad (10)$$

Table 9. Rat lung

		log K	Y Pred	Dev	Clog P
1	Me	−0.21	−0.47	0.25	0.13
2	C_2H_5	0.02	−0.14	0.15	0.66
3	C_3H_7	0.23	0.20	0.03	1.18
4	C_4H_9	0.41	0.53	−0.12	1.71
5	C_5H_{11}	0.53	0.86	−0.33	2.24
6	C_6H_{13}	0.83	1.19	−0.37	2.77
7	C_7H_{15}	1.28	1.53	−0.25	3.30
8	C_8H_{17}	2.10	1.86	0.24	3.83
9	C_9H_{19}	2.59	2.19	0.39	4.36

Table 10. Rat liver

		log K	Y Pred	Dev	Clog P
1	Me	0.44	0.17	0.27	0.13
2	C_2H_5	0.59	0.40	0.19	0.66
3	C_3H_7	0.53	0.64	−0.10	1.18
4	C_4H_9	0.69	0.87	−0.18	1.71
5	C_5H_{11}	0.82	1.11	−0.29	2.24
6	C_6H_{13}	1.18	1.34	−0.16	2.77
7	C_7H_{15}	1.31	1.57	−0.27	3.30
8	C_8H_{17}	1.97	1.81	0.16	3.83
9	C_9H_{19}	2.41	2.04	0.37	4.36

$n = 9$, $r^2 = 0.871$, $s = 0.265$, $q^2 = 0.749$.

Rat kidney tissue[13] (Table 11):

$$\log K = 0.50(\pm 0.10)\,\text{C}\log P - 0.03(\pm 0.27) \quad (11)$$

$n = 8$, $r^2 = 0.961$, $s = 0.170$, $q^2 = 0.933$, outlier: C_5H_{11}.

Rat stomach tissue[13] (Table 12):

$$\log K = 0.74(\pm 0.09)\,\text{C}\log P - 0.92(\pm 0.24) \quad (12)$$

$n = 9$, $r^2 = 0.982$, $s = 0.157$, $q^2 = 0.965$.

Rat pancreas tissue (Table 13):[13]

$$\log K = 0.72(\pm 0.13)\,\text{C}\log P - 0.93(\pm 0.34) \quad (13)$$

$n = 9$, $r^2 = 0.961$, $s = 0.226$, $q^2 = 0.921$.

Rat spleen tissue[13] (Table 14):

$$\log K = 0.61(\pm 0.17)\,\text{C}\log P - 0.59(\pm 0.44) \quad (14)$$

$n = 9$, $r^2 = 0.914$, $s = 0.288$, $q^2 = 0.830$.

Table 11. Rat kidney

		log K	Y Pred	Dev	Clog P
1	Me	0.10	0.03	0.07	0.13
2	C_2H_5	0.27	0.30	−0.03	0.66
3	C_3H_7	0.66	0.56	0.10	1.18
4	C_4H_9	0.87	0.83	0.04	1.71
5*	C_5H_{11}	0.78	1.10	−0.32	2.24
6	C_6H_{13}	1.06	1.36	−0.30	2.77
7	C_7H_{15}	1.47	1.63	−0.16	3.30
8	C_8H_{17}	2.00	1.90	0.11	3.83
9	C_9H_{19}	2.34	2.16	0.18	4.36

*Outlier.

Table 12. Rat stomach

		log K	Y Pred	Dev	Clog P
1	Me	−0.59	−0.83	0.24	0.13
2	C_2H_5	−0.52	−0.43	−0.09	0.66
3	C_3H_7	−0.14	−0.04	−0.10	1.18
4	C_4H_9	0.34	0.35	−0.02	1.71
5	C_5H_{11}	0.51	0.75	−0.24	2.24
6	C_6H_{13}	1.21	1.14	0.07	2.77
7	C_7H_{15}	1.65	1.53	0.12	3.30
8	C_8H_{17}	1.83	1.93	−0.09	3.83
9	C_9H_{19}	2.42	2.32	0.11	4.36

Table 13. Rat pancreas

		log *K*	Y Pred	Dev	Clog *P*
1	Me	−0.49	−0.84	0.34	0.13
2	C_2H_5	−0.42	−0.45	0.03	0.66
3	C_3H_7	−0.16	−0.07	−0.09	1.18
4	C_4H_9	0.16	0.31	−0.15	1.71
5	C_5H_{11}	0.40	0.70	−0.29	2.24
6	C_6H_{13}	0.96	1.08	−0.12	2.77
7	C_7H_{15}	1.33	1.46	−0.13	3.30
8	C_8H_{17}	1.98	1.85	0.14	3.83
9	C_9H_{19}	2.50	2.23	0.27	4.36

Table 14. Rat spleen

		log *K*	Y Pred	Dev	Clog *P*
1	Me	−0.24	−0.51	0.27	0.13
2	C_2H_5	−0.06	−0.19	0.13	0.66
3	C_3H_7	0.12	0.13	−0.01	1.18
4	C_4H_9	0.34	0.45	−0.11	1.71
5	C_5H_{11}	0.46	0.77	−0.31	2.24
6	C_6H_{13}	0.81	1.09	−0.28	2.77
7	C_7H_{15}	1.14	1.41	−0.28	3.30
8	C_8H_{17}	1.86	1.73	0.13	3.83
9	C_9H_{19}	2.51	2.05	0.45	4.36

Table 15. Rat gut

		log *K*	Y Pred	Dev	Clog *P*
1	Me	−0.22	−0.44	0.22	0.13
2	C_2H_5	−0.14	−0.13	−0.01	0.66
3	C_3H_7	0.08	0.18	−0.10	1.18
4	C_4H_9	0.49	0.49	0.00	1.71
5	C_5H_{11}	0.60	0.80	−0.20	2.24
6	C_6H_{13}	1.09	1.11	−0.02	2.77
7	C_7H_{15}	1.30	1.42	−0.11	3.30
8	C_8H_{17}	1.68	1.73	−0.05	3.83
9	C_9H_{19}	2.31	2.04	0.27	4.36

Rat gut tissue[13] (Table 15):

$$\log K = 0.59(\pm 0.10)\,\mathrm{C}\log P - 0.52(\pm 0.25) \qquad (15)$$

$n = 9$, $r^2 = 0.969$, $s = 0.164$, $q^2 = 0.932$.

Rat muscle tissue[13] (Table 16):

$$\log K = 0.55(\pm 0.07)\,\mathrm{C}\log P - 0.46(\pm 0.19) \qquad (16)$$

$n = 9$, $r^2 = 0.980$, $s = 0.124$, $q^2 = 0.961$.

Table 16. Rat muscle

		log *K*	Y Pred	Dev	Clog *P*
1	Me	−0.22	−0.39	0.17	0.13
2	C_2H_5	−0.07	−0.10	0.02	0.66
3	C_3H_7	0.21	0.20	0.01	1.18
4	C_4H_9	0.34	0.49	−0.15	1.71
5	C_5H_{11}	0.61	0.78	−0.18	2.24
6	C_6H_{13}	1.05	1.07	−0.02	2.77
7	C_7H_{15}	1.32	1.37	−0.05	3.30
8	C_8H_{17}	1.71	1.66	0.05	3.83
9	C_9H_{19}	2.10	1.95	0.15	4.36

Table 17. Rat adipose tissue

		log *K*	Y Pred	Dev	Clog *P*
1	Me	−0.46	−0.61	0.15	0.13
2	C_2H_5	−0.12	−0.18	0.05	0.66
3	C_3H_7	0.19	0.26	−0.07	1.18
4	C_4H_9	0.47	0.69	−0.21	1.71
5	C_5H_{11}	0.86	1.12	−0.26	2.24
6	C_6H_{13}	1.82	1.55	0.27	2.77
7	C_7H_{15}	2.09	1.98	0.11	3.30
8	C_8H_{17}	2.33	2.41	−0.08	3.83
9	C_9H_{19}	2.89	2.85	0.04	4.36

Rat adipose tissue[13] (Table 17):

$$\log K = 0.82(\pm 0.11)\,\mathrm{C}\log P - 0.71(\pm 0.28) \qquad (17)$$

$n = 9$, $r^2 = 0.979$, $s = 0.185$, $q^2 = 0.969$.

Rat skin tissue[13] (Table 18):

$$\log K = 0.59(\pm 0.18)\,\mathrm{C}\log P - 0.35(\pm 0.48) \qquad (18)$$

$n = 8$, $r^2 = 0.914$, $s = 0.303$, $q^2 = 0.825$, outlier: C_5H_{11}.

Rat heart tissue[13] (Table 19):

$$\log K = 0.58(\pm 0.05)\,\mathrm{C}\log P - 0.50(\pm 0.14) \qquad (19)$$

$n = 9$, $r^2 = 0.989$, $s = 0.093$, $q^2 = 0.978$.

Rat brain tissue[13] (Table 20):

$$\log K = 0.61(\pm 0.13)\,\mathrm{C}\log P - 0.52(\pm 0.34) \qquad (20)$$

$n = 8$, $r^2 = 0.959$, $s = 0.211$, $q^2 = 0.914$, outlier: C_5H_{11}.

Table 18. Rat skin

		log *K*	Y Pred	Dev	Clog *P*
1	Me	0.05	−0.28	0.33	0.13
2	C_2H_5	0.10	0.03	0.06	0.66
3	C_3H_7	0.26	0.35	−0.09	1.18
4	C_4H_9	0.36	0.66	−0.30	1.71
5*	C_5H_{11}	0.36	0.97	−0.61	2.24
6	C_6H_{13}	1.17	1.29	−0.12	2.77
7	C_7H_{15}	1.19	1.60	−0.41	3.30
8	C_8H_{17}	2.07	1.91	0.16	3.83
9	C_9H_{19}	2.60	2.23	0.37	4.36

*Outlier.

Table 19. Rat heart

		log *K*	Y Pred	Dev	Clog *P*
1	Me	−0.26	−0.42	0.16	0.13
2	C_2H_5	−0.14	−0.12	−0.03	0.66
3	C_3H_7	0.09	0.19	−0.10	1.18
4	C_4H_9	0.49	0.49	−0.01	1.71
5	C_5H_{11}	0.68	0.80	−0.12	2.24
6	C_6H_{13}	1.10	1.11	0.00	2.77
7	C_7H_{15}	1.37	1.41	−0.04	3.30
8	C_8H_{17}	1.75	1.72	0.03	3.83
9	C_9H_{19}	2.11	2.02	0.09	4.36

Table 20. Rat brain

		log *K*	Y Pred	Dev	Clog *P*
1	Me	−0.22	−0.44	0.22	0.13
2	C_2H_5	−0.12	−0.12	0.00	0.66
3	C_3H_7	0.15	0.21	−0.05	1.18
4	C_4H_9	0.41	0.53	−0.12	1.71
5*	C_5H_{11}	0.40	0.86	−0.46	2.24
6	C_6H_{13}	1.11	1.18	−0.07	2.77
7	C_7H_{15}	1.17	1.50	−0.33	3.30
8	C_8H_{17}	1.90	1.83	0.07	3.83
9	C_9H_{19}	2.44	2.15	0.29	4.36

*Outlier.

Table 21. Rat testis

		log *K*	Y Pred	Dev	Clog *P*
1	Me	−0.16	−0.36	0.20	0.13
2	C_2H_5	−0.10	−0.08	−0.02	0.66
3	C_3H_7	0.21	0.20	0.01	1.18
4	C_4H_9	0.41	0.49	−0.07	1.71
5	C_5H_{11}	0.60	0.77	−0.17	2.24
6	C_6H_{13}	0.91	1.05	−0.14	2.77
7	C_7H_{15}	1.32	1.34	−0.02	3.30
8	C_8H_{17}	1.63	1.62	0.01	3.83
9	C_9H_{19}	2.11	1.90	0.21	4.36

Rat testis tissue[13] (Table 21):

$$\log K = 0.54(\pm 0.08)\,\mathrm{C}\log P - 0.43(\pm 0.21) \qquad (21)$$

$n = 9$, $r^2 = 0.972$, $s = 0.141$, $q^2 = 0.942$.

Rat plasma. Ratio of bound to unbound chemical[13] (Table 22):

$$\log K = 0.90(\pm 0.08)\,\mathrm{C}\log P - 1.88(\pm 0.21) \qquad (22)$$

$n = 8$, $r^2 = 0.993$, $s = 0.105$, $q^2 = 0.987$, outlier: CH_3.

Rat red blood cells. Ratio of cell concentration to that unbound in plasma[13] (Table 23):

$$\log K = 0.48(\pm 0.12)\,\mathrm{C}\log P - 0.37(\pm 0.31) \qquad (23)$$

$n = 9$, $r^2 = 0.930$, $s = 0.206$, $q^2 = 0.861$.

From this excellent study we see that the calculated octanol water partition does an excellent job, without the trouble of measuring the penetration of Caco-2 cell layers. Of interest is the fact that except for QSAR 22. The other QSAR have similar slopes and intercepts.

Table 22. Rat plasma

		log *K*	Y Pred	Dev	Clog *P*
1	Me	—	−1.77	—	0.13
2	C_2H_5	−1.40	−1.29	−0.11	0.66
3	C_3H_7	−0.80	−0.81	0.02	1.18
4	C_4H_9	−0.17	−0.34	0.16	1.71
5	C_5H_{11}	0.03	0.14	−0.11	2.24
6	C_6H_{13}	0.66	0.61	0.04	2.77
7	C_7H_{15}	1.15	1.09	0.06	3.30
8	C_8H_{17}	1.59	1.57	0.02	3.83
9	C_9H_{19}	1.95	2.04	−0.09	4.36

Table 23. Rat red blood cells

		log *K*	Y Pred	Dev	Clog *P*
1	Me	0.00	−0.31	0.31	0.13
2	C_2H_5	0.02	−0.05	0.07	0.66
3	C_3H_7	0.06	0.20	−0.14	1.18
4	C_4H_9	0.23	0.46	−0.23	1.71
5	C_5H_{11}	0.64	0.71	−0.08	2.24
6	C_6H_{13}	0.75	0.97	−0.22	2.77
7	C_7H_{15}	1.18	1.23	−0.05	3.30
8	C_8H_{17}	0.60	1.48	0.12	3.83
9	C_9H_{19}	1.96	1.74	0.22	4.36

2.3. Metabolism

The importance of metabolism in drug design was recognized even before the appellation 'rational' could be applied. In many cases, metabolism was utilized to convert a pro-drug to its active form (e.g., action of esterases on the ester of a drug), but more commonly, one wants to avoid drug candidates that will quickly lose activity through metabolism or worse, made toxic thereby. In an earlier examination of the QSAR approach to understanding metabolic processes,[4] we focused on equations dealing with both phase I and phase II metabolism. The most important enzyme in metabolism is the Cytochrome P-450 class. It is noteworthy that out of 90 QSAR on P-450, both simple binding and oxidation reactions, 55 contain a positive log *P* term. We also have three QSAR with positive log *P* terms that correlate the induction of P-450 by various compounds, indicating that hydrophobic drugs might induce their own destruction. The QSAR of P450 has recently been reviewed.[14]

2.4. Elimination

In considering excretion of organic compounds, we shall focus on examples where metabolism is not involved; that is, excretion of the unchanged drug. Compounds that are rather strongly ionized (e.g., sulfonamides require an electronic term in addition to log *P* to account for rate of elimination).

Excretion of phenols from Daphnia magna. Data from Gerritsen et al.[15] (Table 24):

Table 24. Excretions of X-C6H4OH from *Daphnia magna*

		log *K*	Y Pred	Dev	Clog *P*
1	4-$CHMeC_2H_5$	0.83	0.78	0.05	3.43
2	4-CMe_3	0.87	0.84	0.03	3.30
3*	4-$C(Me)_2C_2H_5$	−0.09	0.6	−0.68	3.83
4	2,4-CMe_3	0.01	0.1	−0.09	4.93
5	4-$C(C_2H_5)_2C_3H_7$	−0.28	−0.12	−0.15	5.42
6	4-Nonyl	−0.33	−0.48	0.16	6.21

*Outlier.

$$\log K = -0.45(\pm 0.18)\,\mathrm{C}\log P + 2.34(\pm 0.84) \qquad (24)$$

$n = 5$, $r^2 = 0.957$, $s = 0.140$, $q^2 = 0.850$, outlier: 4-*t*-butylphenol (not excreted as fast as predicted).

Fraction of miscellaneous anti-hypertensive drug excreted unchanged after IV injection in humans. Hinderling et al.[16] (Table 25):

$$\log K = -0.54(\pm 0.15)\,\mathrm{C}\log P + 0.04(\pm 0.29) \qquad (25)$$

$n = 11$, $r^2 = 0.886$, $s = 0.228$, $q^2 = 0.848$, outliers: penbutolol, pindolol, practolol.

Excretion of miscellaneous pesticides from catfish. Data from Ellgehausen et al.[17] (Table 26):

$$\log K = -0.67(\pm 0.13)\log P + 2.95(\pm 0.44) \qquad (26)$$

$n = 7$, $r^2 = 0.973$, $s = 0.193$, $q^2 = 0.926$, outlier: 2,4-dichlorophenoxyacetic acid.

K is related to the half-life of the chemical in the fish. Thus, we see from three quite different types of studies, that the coefficients with the $\log P$ term are quite similar and negative.

Parameters other than $\log P$ may be required if significant ionization is involved. This can be illustrated with data on the excretion of miscellaneous compounds from rats

Table 25. Excretion of hypertensive drugs from human

		log *K*	Y Pred	Dev	Clog *P*
1*	Penbutolol	—	−2.14	—	4.04
2	Bufuralol	−1.70	−1.80	0.10	3.40
3	Tolamolol	−1.30	−1.09	−0.21	2.10
4	Propranolol	−1.40	−1.44	0.05	2.75
5	Alprenolol	−1.70	−1.39	−0.31	2.65
6	Oxprenolol	−0.96	−1.09	0.13	2.09
7	Acebutolol	−0.39	−0.88	0.49	1.71
8	Timolol	−0.92	−0.81	−0.11	1.58
9	Metoprolol	−0.82	−0.69	−0.14	1.35
10*	Pindolol	−0.30	−0.86	0.56	1.67
11	Atenolol	−0.03	0.10	−0.13	−0.11
12	Nadolol	−0.12	−0.16	0.04	0.38
13	Sotalol	0.00	−0.08	0.08	0.23

*Outliers.

Table 26. Excretion of miscellaneous pesticides from catfish

		log *K*	Y Pred	Dev	Clog *P*
1	P,P′-DDP	−1.28	−1.19	−0.10	6.19
2	Terbutryn	0.47	0.45	0.02	3.74
3	Metolachlor	0.96	0.86	0.10	3.13
4	Atrazine	1.43	1.11	0.32	2.75
5	Monuron	1.32	1.56	−0.24	2.08
6	Thiazafluron	1.65	1.71	−0.06	1.85
7	CGA-48-988	1.80	1.85	−0.05	1.65
8*	2,4-D	2.18	1.07	1.11	2.81

*Outliers.

Table 27. Excretion of miscellaneous sulfonamides from rat

		log *K*	Y Pred	Dev	DpK_a	Mlog *P*
1*	Sulfamine	−1.18	−2.14	0.96	0.00	−0.62
2	Acetoxulfamine	−0.19	−0.29	0.10	5.05	−0.96
3*	Sulfathiazole	−0.63	−1.37	0.74	3.35	0.05
4	Diazine	−1.14	−0.99	−0.15	4.30	−0.09
5	Merazine	−1.17	−1.36	0.19	3.52	0.14
6*	Isoxazole	−0.61	−1.04	0.43	5.83	1.01
7	Phenazole	−1.55	−1.73	0.18	4.54	1.52
8	Methoxypyridazine	−1.55	−1.49	−0.06	3.40	0.32
9	Dimethoxine	−1.92	−1.83	−0.09	4.40	1.63
10	Isomezole	−1.34	−1.37	0.03	4.64	0.89
11	Monomethoxine	−1.41	−1.20	−0.21	4.42	0.41

*Outliers.

Data from Yamazaki et al.[18] (Table 27):

$$\log k = -0.51(\pm 0.20)\log P + 0.33(\pm 0.31)\mathrm{p}K_a - 2.45(\pm 1.35) \qquad (27)$$

$n = 8$, $r^2 = 0.912$, $s = 0.178$, $q^2 = 0.712$, outliers: sulfamine, sulfathiazole, isoxazole.

After correction for ionization, ($\mathrm{p}K_a$ = ionization constant) the $\log P$ term is similar to those in the other examples.

3. Discussion

There has been a recent tendency to refer to ADMET where T stands for toxicology. It is wishful thinking to believe that toxicology can be treated adequately via comparative QSAR. One must force the fact that at the present time, no one knows how to deal with metabolism. Cytochrome P-450 enzymes play the major role in metabolism. We have 96 QSAR for the activity of this varied class of enzymes. We plan to attempt to relate these QSAR to ADME but it is too complex for the current report. While ADME is clearly a most important subject to elucidate and there has been much discussion of the subject, to our knowledge, this is the first attempt to develop a general approach to analyze the subject via QSAR. It is not possible to make sense of ADME in terms of a single compound. For drawing helpful conclusions for drug design one must have the perspective provided by QSAR.

Clearly Clog P from the octanol/water system is a crucial parameter for developing our understanding of ADME. The program from BioByte Corporation developed over the years is of enormous help. Its quality can be seen from the following equation:

$$\log P = 0.96\,\mathrm{C}\log P + 0.071$$

$n = 12,500$, $r^2 = 0.973$, $s = 0.30$.

The above equation holds only for neutral compounds. Useful values are obtained for a set of compounds that contain a common acid function (e.g., COOH), for

example, at a pH of 7.4 where all would be off the value for the partially ionized compound. Of course, if the function is not involved in the crucial step, ionization may not be important or the situation can be dealt with as in the example of QSAR 27.

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