Progress in Drug Research

Progress in Drug Research

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Foreword by the Editor

Volume 54 of *Progress in Drug Research* contains seven review articles and various indices which facilitate the use of these monographs and also help to establish PDR as an encyclopaedic source of information. The individual articles contain innumerable references and help the active researcher in finding the information he or she is interested in.

The first article of this volume deals with the Caco-2 cell permeability and human gastrointestinal absorption. Other contributions are devoted to pharmacology of appetite suppression – a problem of great actuality – or present an overview on progress made in the research of serotonin, dopamine and norepinephrine transporters in the central nervous system. Also, neuropeptides, which are summarily treated in view of the search for novel pharmaceutically active substances, is dealt with as well as regulation of NMDA receptors by ethanol. Troglitazone and emerging glitazones show new avenues for potential therapeutic benefits beyond glycemic control. The corresponding review is of great interest in the field of diabetic disorders. A final chapter on application of developmental biology to medicine and animal agriculture demonstrates the practical importance of modern genetic research

In summary, all chapters in this volume prove to be a valuable impulse for further research leading to new drugs.

In the 41 years of PDR's existence, drug research has undergone drastic changes; the original purpose of these monographs, however, remained unchanged: dissemination of information about actual trends and crucial points in drug research. In line with modern drug research, PDR now covers almost all scientific disciplines.

The editor is anxious to maintain the high standards of PDR and is grateful to the authors for their comprehensively written review articles. I would also like to thank the members of the Board of Advisors for their advice and for suggesting current topics. The reviewers have greatly helped to improve these monographs, and I am grateful to them as well.

I would also like to thank Birkhäuser Publishing Inc., and in particular Daniela Brunner, Ruedi Jappert, Bernd Luchner, Eduard Mazenauer and Gregor Messmer, with whom I have a harmonious and rewarding relationship. My very special thanks go to Mr. Hans-Peter Thür, Birkhäuser

Publishing's CEO. Over a few decades I have and still do enjoy Mr. Thür's constant support and encouragement to continue the editorship of PDR.

Basel, May 2000

Dr. E. Jucker

Contents

Progress in Drug Research, Vol. 54 (E. Jucker, Ed.)

Caco-2 cell permeability vs human gastro-intestinal absorption: QSPR analysis[1]

By Shijun Ren and Eric J. Lien

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[1]Part of this work has been presented at a poster session of the AAPS Western Regional Meeting, San Diego, California, USA, April 29–30, 1999

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Eric J. Lien

received his Ph.D. from the University of California San Francisco Medical Center in 1966. After his postdoctoral training at Pomona College, he joined the University of Southern California in 1968 as a faculty member. Professor Lien's research interests include structure-activity relationship and drug design, physical organic chemistry and natural products. He has served as a consultant to various government agencies, universities and private cooperations. His most recent work deals with the evolution of biomacromolecules, from thermoneutrons to living organisms.

Summary

The aim of this study is to elucidate quantitative structure-permeability relationship (QSPR) of various organic molecules through Caco-2 cells, and to ascertain the relationship between gastrointestinal (GI) absorption in humans and Caco-2 cell permeability. Caco-2 cell permeability and human GI absorption data were obtained from the literature. The maximum hydro-

gen bond-forming capacity corrected for intra-molecular H-bonding (H_b^c) and Lien's QSAR model were used in this study. The latest CQSAR software was utilized in calculating the logarithm of partition coefficient in octanol/water (Clog P) and in deriving all regression equations. For 51 compounds, a significant correlation was obtained between Caco-2 cell permeability (log $P_{caco\text{-}2}$) and H_b^c, octanol/PBS (phosphate buffered saline, pH 7.4) distribution coefficient (log D_{oct}), log MW and an indicator variable (I) for the charge, with a correlation coefficient of 0.797. When these compounds were divided into three subgroups, namely neutral, cationic and anionic compounds, much better correlations (r = 0.968, 0.915 and 0.931, respectively) were obtained using different combinations of various physicochemical parameters. A plot of human GI absorption vs. Caco-2 cell permeability obtained from different laboratories reveals that Caco-2 cell permeability cannot be used to precisely predict human GI absorption for compounds with $P_{caco\text{-}2}$ below 5×10^{-6} cm/s, due to interlaboratory and experimental variabilities, and the lack of a simple correlation between human GI absorption and Caco-2 cell permeability. Caco-2 cell permeability may be estimated from the structures of drug molecules using the above-mentioned physicochemical parameters. In general, for compounds with $P_{caco\text{-}2}$ above 5×10^{-6} cm/s, human GI absorption ranges from 50 to 100%. This is generally acceptable for development into oral dosage form. For the compounds with $P_{caco\text{-}2}$ below 5×10^{-6} cm/s, careful interpretation of caco-2 cell permeability and use of internal standard for comparison are recommended. Otherwise, good drug candidates may be excluded due to incorrectly predicted poor absorption.

Contents

Keywords
Caco-2 cells; calculated partition coefficient (Clog P); distribution coefficient (log D_{oct}); hydrogen bonding; oral absorption; permeability; QSAR

Glossary of abbreviations
Clog P, calculated log P; GI, gastrointestinal; H_b^c, the maximum hydrogen bond-forming capacity corrected for intra-molecular hydrogen bonding; log D_{oct}, logarithm of octanol/PBS (phophate buffered saline, pH 7.4) distribution coefficient; log P, logarithm of octanol/water partition coefficient; MW, molecular weight; P_{caco-2}, Caco-2 cell apparent permeability coefficient; QSAR, quantitative structure-activity relationship; QSPR, quantitative structure-permeability relationship

1 Introduction

Oral administration is the most important and preferred route for low molecular weight (< 500 Da) conventional drugs. The overall bioavailability of an orally administered drug depends on many factors, including physicochemical properties of the drug as well as various physiological and biochemical barriers (such as metabolic enzymes, drug transporters, and the presence of multidrug resistance (MDR) P-glycoprotein). In recent years, in order to elucidate the role of various physiological and biochemical barriers to drug absorption, and to rapidly predict human gastrointestinal (GI) absorption in high throughput screening (HTS), Caco-2 cell line (a cell line derived from a human colorectal carcinoma) has been used as an *in vitro* model to study human GI absorption of drugs which cross the intestinal epithelium by transcellular or paracellular passive diffusion [1–6]. The demonstration of a good correlation between the extent of oral drug absorption in humans and rates of transport across the Caco-2 cell monolayers by Artursson and Karlsson [2] has further contributed to the widespread use of these cells as an *in vitro* model for GI drug absorption. This suggests that human GI absorption may be "predicted" by using *in vitro* Caco-2 permeability. Furthermore, methods for predicting Caco-2 cell permeability or drug GI absorption using different physicochemical properties of the drugs have been examined [7–13]. Lien's group has also reported a general model to correlate membrane permeability with physicochemical properties, namely hydrophobicity as measured by octanol/water partition coefficient

(log P), molecular weight (MW) as a measurement of molecular size, and hydrogen bonding capacity (H_b) [14–20].

$$\text{Log (permeability)} = -k_1 \cdot (\log P)^2 + k_2 \cdot \log P + n \cdot \log MW + q \cdot H_b + k_3 \quad (1)$$

In Eq. 1, when log P values lie in a relatively narrow range, the $-k_1 \cdot (\log P)^2$ term approaches zero, then log (permeability) becomes linearly dependent on log P, log MW and H_b. Van de Waterbeemd and Camenisch [11] have used a similar function to represent permeability-physicochemical property relationship.

$$\text{Permeability} = f\,(\text{lipophilicity, molecular size, H-bonding capacity, charge}) \quad (2)$$

When distribution coefficients (log D) or apparent partition coefficients (log P') instead of log P are used, the effect of difference in charge is included in the lipophilicity term (log D or log P'). When charge is a constant for all compounds analyzed, the charge term becomes part of the constant term.

Figure 1 shows the inter-relationships among physicochemical properties, Caco-2 cell permeability and human GI absorption in drug design and development.

Studies by Chiou et al. [21–23] demonstrated that rat may serve as a useful animal model to predict the extent of GI absorption in humans following oral administration of drugs in a solution or rapidly released dosage form. Recently, Caco-2 cell monolayers have been generally accepted as a primary absorption screening tool in the early stage of drug development. There are several examples of successful application of Caco-2 cell for prediction of or correlation with human GI absorption [2, 7]. However, different laboratories have reported very different threshold values of apparent permeability coefficients ($P_{caco\text{-}2}$) for poorly and well-absorbed compounds, and quite different $P_{caco\text{-}2}$ values for the same compound. These prompted this systematic investigation.

The purpose of this study is to elucidate QSPR of diverse organic compounds through Caco-2 cell monolayers, and to ascertain the relationship between Caco-2 cell permeability and human GI absorption. A more coherent cutoff threshold value of $P_{caco\text{-}2}$ for poorly and well-absorbed compounds will be suggested.

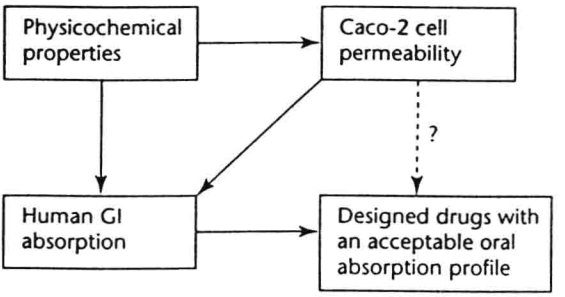

Fig. 1.
The interrelationships among physicochemical properties, Caco-2 cell permeability and human GI absorption in drug design and development.

2 Methods

Caco-2 cell permeability and human GI absorption data were obtained from the literature [2, 7, 24–29]. The latest CQSAR program [30] was utilized in calculating the Clog P (calculated log P) values, and in deriving all regression equations.

The maximum hydrogen bonding capacity corrected for intramolecular hydrogen-bonding (H_b^c) was calculated based on the following rules [14–20]: (a) the number of hydrogen donors is equal to the number of hydrogen atoms which can form hydrogen bonds as donors; (b) the number of hydrogen acceptors is equal to the lone electron pairs of a given group. For example, for –Ö̈H group the number of hydrogen donor is one, and there are two lone electron pairs on oxygen. Therefore, the total hydrogen bonding for –Ö̈H group is equal to 3̈; (c) if there are any intramolecular hydrogen bonds within a molecule, the number of intra-molecular hydrogen bonding will be subtracted from the total number of hydrogen bonding. For example, salicylic acid has one intramolecular hydrogen bond involving one hydrogen donor and one hydrogen acceptor, by subtracting 2 from the total number of 8, H_b^c of 6 is obtained. The atomic distances were obtained by using the HyperChem program [31] after performing geometry optimization and energy

minimization for the molecule. If the hydrogen donor and acceptor form a five- or six-member pseudo-ring and the atomic distance between two hetero-atoms (N, O) is around 2.63 to 3.10 Å [32], the intramolecular hydrogen bonding is assigned for the molecule.

3 Results and discussion

3.1 Correlation of Caco-2 cell permeability with physicochemical properties

Physicochemical properties (MW, H_b^c, log D_{oct}, Clog P, log P and pK_a), Caco-2 cell apparent permeability coefficients, and percent human GI absorption are presented in Table 1. For 51 diverse compounds, the following stepwise equations were obtained from the regression analysis.

$$\text{Log } P_{caco\text{-}2} = -0.126\ (0.042)\ H_b^c + 1.900\ (0.400) \quad (3)$$
$$n = 51,\ r = 0.648,\ r^2 = 0.420,\ s = 0.567,\ F_{1,49} = 35.53,\ p < 0.0005$$

$$\text{Log } P_{caco\text{-}2} = -0.142\ (0.038)\ H_b^c - 0.374\ (0.195)\ I + 2.169\ (0.381) \quad (4)$$
$$n = 51,\ r = 0.746,\ r^2 = 0.556,\ s = 0.502,\ F_{2,48} = 30.07,\ p < 0.0005;$$
$$F_{1,48} = 14.68,\ p < 0.0005$$

$$\text{Log } P_{caco\text{-}2} = -0.111\ (0.042)\ H_b^c - 0.326\ (0.185)\ I + 0.151\ (0.104)$$
$$\log D_{oct} + 1.819\ (0.428) \quad (5)$$
$$n = 51,\ r = 0.790,\ r^2 = 0.624,\ s = 0.467,\ F_{3,47} = 25.99,\ p < 0.0005;$$
$$F_{1,47} = 8.47,\ p < 0.01$$

$$\text{Log } P_{caco\text{-}2} = -0.094\ (0.050)\ H_b^c - 0.334\ (0.185)\ I + 0.202\ (0.136) \log D_{oct}$$
$$- 0.679\ (1.168) \log MW + 3.304\ (2.589) \quad (6)$$
$$n = 51,\ r = 0.797,\ r^2 = 0.635,\ s = 0.465,\ F_{4,46} = 19.98,\ p < 0.0005;$$
$$F_{1,46} = 1.35,\ p < 0.25$$

$$\text{Log } P_{caco\text{-}2} = -0.109\ (0.039)\ H_b^c - 0.358\ (0.150)\ I + 0.310\ (0.111) \log D_{oct}$$
$$- 1.349\ (0.924) \log MW + 4.949\ (2.062) \quad (7)$$
$$n = 46,\ r = 0.893,\ r^2 = 0.798,\ s = 0.357,\ F_{4,41} = 40.37,\ p < 0.0005;$$
$$F_{1,41} = 8.52,\ p < 0.01$$

$$\text{Log } P_{caco\text{-}2} = -0.146\ (0.073)\ H_b^c - 0.342\ (0.235)\ I - 0.002\ (0.140)\ \text{Clog P}$$
$$+ 0.509\ (1.462) \log MW + 0.970\ (2.987) \quad (8)$$
$$n = 50,\ r = 0.749,\ r^2 = 0.561,\ s = 0.506,\ F_{4,45} = 14.40,\ p < 0.0005$$

Table 1.
The physicochemical properties, Caco-2 cell permeability (log P_{caco-2}) and percent GI absorption for 51 compounds.

	Compounds	Log P_{caco-2} obsd.[a]	Log P_{caco-2} calcd.	% absorbed[a]	MW	H_b[c]	Clog P[e]	Log D_{oct}[a]	I	log P[f]	pKa[g]
1	Griseofulvin	1.563	1.346[b]	Irregular	352.8	12	1.52	2.47	0	2.18	
2	Arninopyrine	1.562	1.722[b]	100	231.3	5	1.00	0.63	0	1.00	5.0
3	Piroxicam	1.551	1.189[c]	100	331.4	11	1.89	–0.07	–1	1.98	2.33, 5.07
4	Diazepam	1.524	1.687[b]	100	284.8	4	3.16	2.58	0	2.99	3.4
5	Caffeine	1.489	0.996[b]	100	194.2	8	–0.06	0.02	0	-0.07	0.6, 14.0
6	Nevirapine	1.479	1.373[b]	> 90	266.3	7	2.53	1.81	0		
7	Phenytoin	1.427	1.558[d]	90	252.3	8	2.09	2.26	1	2.47	8.3
8	Alprenolol	1.403	1.357[d]	93	249.3	5	2.65	1.38	1	2.89	9.7
9	Testosterone	1.396	1.457[b]	100	288.4	5	3.22	2.91	0	3.32	
10	Phencyclidine	1.393	1.593[d]		248.4	1	5.10	1.31	1	3.63	8.5[i]
11	Desipramine	1.387	1.528[d]	> 95	266.4	3	4.47	1.57	1	4.90	10.2
12	Metoprolol	1.375	0.763[d]	95	267.4	7	1.35	0.51	1	1.88	9.7
13	Progesterone	1.375	1.393[b]		314.5	4	3.78	3.48	0	3.87	
14	Salicylic acid	1.342	1.035[c]	100	138.1	6	2.19	–1.44	–1	2.26	3.0
15	Clonidine	1.338	1.138[d]	100	230.1	5	1.41	0.78	1	1.43	8.1
16	Propranolol	1.338	1.406[d]	90	259.3	5	2.19	1.55	1	2.98	9.5
17	Corticosterone	1.326	1.318[b]	100	346.5	8	2.32	1.78	0	1.94	
18	Warfarin	1.324	1.418[c]	98	308.3	9	2.62	0.64	–1	2.70	5.1
19	Indomethacin	1.310	1.352[c]	100	357.7	10	3.88	1.00	–1	4.27	4.5
20	Chlorpromazine	1.299	1.591[d]	Erratic	318.9	2	5.78	1.86	1	5.19	9.3
21	Meloxicam	1.290	1.189[c]	90	351.4	11	2.28	0.03	–1	3.01	3.4
22	Nicotine	1.288	1.435[d]	100	162.2	2	0.90	0.41	1	1.17	3.1, 8.2
23	Estradiol	1.229	1.044[b]	Rapidly metabolized	272.4	6	3.73	2.24	0	4.01	
24	Pindolol	1.223	0.671[d]	95	248.3	7	1.11	0.19	1	1.75	9.5
25	Telmisartan	1.179	1.418[c]	90	514.6	9	7.26	2.41	–1		
26	Hydrocortisone	1.146	1.301[b]	89	362.5	11	1.70	1.48	0	1.61	

Tasble 1 continued

27	Timolol	1.107	0.181[dh]	72	328.4	10	1.53	0.03	1	1.83	9.2
28	Dexamethasone	1.086	1.300[b]	100	392.5	11	1.75	2.16	0	2.01	
29	Scopolamine	1.072	0.326[d]	100	303.4	10	0.30	0.21	1		7.6
30	Dopamine	0.970	0.581[d]		153.2	7	0.17	−0.80	1		8.87, 10.63
31	Labetalol	0.969	0.841[d]	90	316.4	9	2.50	1.24	1		9.5
32	Acetylsalicylic acid	0.959	1.259[c]	100	180.2	7	1.02	−2.25	−1	1.19	3.50
33	Bremazocine	0.904	0.888[b]		351.9	7	3.77	1.66	0		
34	Zidovudine	0.841	0.952[b]	100	267.2	10	0.04	−0.58	0	0.05	
35	Urea	0.659	0.844[d]		60.1	8	−2.11	−1.64	1	−2.11	
36	Uracil	0.627	0.611[d]		112.1	8	−1.06	−1.11	1	−1.07	9.45
37	Nadolol	0.589	0.597[d]		309.4	9	0.33	0.68	1	0.71	9.67
38	Sucrose	0.233	0.106[b]		342.3	20	−3.09	−3.34	0	−3.01	
39	Cimetidine	0.137	0.269[d]	95	252.3	9	0.35	−0.36	1	0.40	6.9
40	Methylscopolamine	−0.161	−0.341[d]		318.5	10	−5.48j	−1.14	1		
41	Hydrochlorothiazide	−0.292	−0.147[d]	90	297.7	15	−0.40	−0.12	1	−0.07	7.9, 9.2
42	Atenolol	−0.276	−0.273[d]	50	266.3	10	−0.11	−1.29	1	0.16	9.6
43	Acebutalol	−0.292	0.040[d]	90	336.4	11	1.70	−0.09	1	1.71	9.4
44	Terbutaline	−0.328	0.025[d]	73	225.3	9	0.48	−1.07	1	0.08	8.8, 10.1, 11.2
45	Ranitidine	−0.310	0.145[d]	50	314.4	10	0.63	−0.12	1	0.27	8.2
46	Pirenzepine	−0.357	−0.245[d]	Poor	424.3	10	−0.89	−0.46	1		
47	Mannitol	−0.420	−0.436[b]	16	182.2	12	−2.05	−2.65	0	−3.10	
48	Ganciclovir	−0.420	−0.409[b]	3	255.2	16	−2.56	−0.10	0	−2.07	
49	Sulfasalazine	−0.523	−0.429[c]	13	394.4	15	3.83	−0.42	−1		2.4, 9.7, 11.8
50	Acyclovir	−0.602	−0.325[b]	20	225.2	15	−2.30	−0.35	0	−1.56	2.3, 9.3[i]
51	Chlorothiazide	−0.721	−0.555[d]	Dose-dependent	295.7	14	−0.31	−1.15	1	−0.24	6.7, 9.5

[a]From [24]; [b]calculated from Eq. (11); [c]calculated from Eq. (20); [d]calculated from Eq. (16); [e]calculated using the CQSAR database [30]; [f]measured log P values from the CQSAR database [30]; [g]from the CQSAR database [30]; [h]a statistical outlier, excluded from Eq. (16); [i]from [33]; [j]estimated value using the fragment constant (π) values of $-N(CH_3)_2$ and $-N^+(CH_3)_3$ in [34] and Clog P value of scopolamine.

The statistical parameters describing the regression are n, the number of data points; r, the correlation coefficient; and s, the standard deviation. The numbers in parentheses are 95% confidence intervals of coefficients in the equations. I is an indicator variable for the charge (I = 1 for the positively charged compounds; I = 0 for the neutral compounds; I = -1 for the negatively charged compounds). From Eqs. (3–6), one can see that the use of H_b^c, I, log D_{oct} and log MW does not give a very high correlation coefficient (r = 0.797). H_b^c is the most important contributor to Caco-2 cell permeability, followed by I, log D_{oct} and log MW. Log $P_{caco\text{-}2}$ negatively depends on H_b^c, I and log MW and positively depends on log D_{oct}. Upon deletion of five statistical outliers (residual > 2s), namely sucrose (No. 38), timolol (No. 27), scopolamine (No. 29), piroxicam (No. 3) and progesterone (No. 13), Eq. (7) was obtained with an improved r and a decreased s. The use of Clog P instead of log D_{oct} resulted in Eq. (8) (n = 50 due to one missing fragment constant for Clog P) with a decreased r as compared to Eq. (6), indicating that log D_{oct} is a better descriptor than Clog P in correlating with Caco-2 permeability of diverse molecules. The squared correlation matrix of the parameters used in the regression analysis is shown in Table 2.

When 51 compounds were divided into three subgroups, namely neutral, cationic and anionic compounds, the following equations were obtained.

Neutral compounds

$$\text{Log } P_{caco\text{-}2} = 0.253\ (0.105)\ \text{Clog P} + 0.650\ (0.267) \tag{9}$$
$$n = 17,\ r = 0.797,\ r^2 = 0.636,\ s = 0.467,\ F_{1,15} = 26.17,\ p < 0.0005$$

$$\text{Log } P_{caco\text{-}2} = 0.313\ (0.096)\ \text{Clog P} - 0.065\ (0.047)\ (\text{Clog P})^2 + 1.004\ (0.334) \tag{10}$$
$$n = 17,\ r = 0.882,\ r^2 = 0.778,\ s = 0.378,\ F_{2,14} = 24.51,\ p < 0.0005$$

$$\text{Clog } P_0 = 2.400\ (1.438 - 7.460)$$

$$\underline{\text{Log } P_{caco\text{-}2} = 0.430\ (0.119)\ \text{Clog P} - 0.130\ (0.038)\ (\text{Clog P})^2 - 0.370\ (0.154)\ H_b^c + 0.018\ (0.007)\ (H_b^c)^2 + 2.817\ (0.906)} \tag{11}$$
$$\underline{n = 17,\ r = 0.968,\ r^2 = 0.937,\ s = 0.217,\ F_{4,12} = 44.54,\ p < 0.0005}$$

$$\underline{\text{Clog } P_0 = 1.651\ (1.265 - 2.180),\ H_b^c{}_0 = 10.190\ (8.659 - 11.774)}$$

$$\text{Log } P_{caco\text{-}2} = 0.142\ (0.234)\ \log D_{oct} + 0.006\ (0.098)\ (\log D_{oct})^2 - 0.113\ (0.369)\ H_b^c + 0.002\ (0.017)\ (H_b^c)^2 + 1.660\ (2.091) \tag{12}$$
$$n = 17,\ r = 0.781,\ r^2 = 0.610,\ s = 0.540,\ F_{4,12} = 4.70,\ p < 0.025$$

Table 2.
The squared correlation matrix showing covariance (r^2) between the physicochemical parameters used in the regression analysis for 51 compounds.

	Clog P	log D_{oct}	log MW	H_b^c	I
Clog P	1.000	0.520	0.180	0.326	0.069
log D_{oct}		1.000	0.178	0.244	0.002
log MW			1.000	0.068	0.048
H_b^c				1.000	0.046
I					1.000

Cationic compounds

$$\text{Log } P_{caco\text{-}2} = -0.165\ (0.058)\ H_b^c + 1.945\ (0.498) \quad (13)$$
$n = 26$, $r = 0.767$, $r^2 = 0.588$, $s = 0.487$, $F_{1,24} = 34.24$, $p < 0.0005$

$$\text{Log } P_{caco\text{-}2} = 0.609\ (0.159)\ \log D_{oct} - 2.248\ (1.007)\ \log MW + 5.919\ (2.406) \quad (14)$$
$n = 26$, $r = 0.862$, $r^2 = 0.743$, $s = 0.393$, $F_{2,23} = 33.24$, $p < 0.0005$

$$\text{Log } P_{caco\text{-}2} = -0.063\ (0.066)\ H_b^c + 0.461\ (0.217)\ \log D_{oct} - 1.627\ (1.155)\ \log MW + 4.952\ (2.492) \quad (15)$$
$n = 26$, $r = 0.884$, $r^2 = 0.781$, $s = 0.370$, $F_{3,22} = 26.22$, $p < 0.0005$; $F_{1,22} = 3.88$, $p < 0.1$

$$\text{Log } P_{caco\text{-}2} = -0.067\ (0.058)\ H_b^c + 0.467\ (0.191)\ \log D_{oct} - 1.775\ (1.023)\ \log MW + 5.301\ (2.209) \quad (16)$$
$n = 25$, $r = 0.915$, $r^2 = 0.837$, $s = 0.325$, $F_{3,21} = 35.87$, $p < 0.0005$

$$\text{Log } P_{caco\text{-}2} = -0.055\ (0.064)\ H_b^c + 0.564\ (0.238)\ \log D_{oct} - 0.126\ (0.143)\ (\log D_{oct})^2 - 2.085\ (1.218)\ \log MW + 6.120\ (2.722) \quad (17)$$
$n = 26$, $r = 0.901$, $r^2 = 0.811$, $s = 0.352$, $F_{4,21} = 22.60$, $p < 0.0005$

$\text{Log } D_{oct_0} = 2.239 \pm \text{infinity}$

$$\text{Log } P_{caco\text{-}2} = -0.102\ (0.103)\ H_b^c + 0.367\ (0.300)\ \text{Clog P} - 0.054\ (0.047)\ (\text{Clog P})^2 - 1.622\ (1.772)\ \log MW + 5.152\ (3.607) \quad (18)$$
$n = 26$, $r = 0.831$, $r^2 = 0.691$, $s = 0.451$, $F_{4,21} = 11.73$, $p < 0.0005$

$\text{Clog } P_0 = 3.417\ (1.364 - 12.717)$

Anionic compounds

$$\text{Log } P_{caco\text{-}2} = -0.157\ (0.179)\ H_b^c + 2.587\ (1.803) \quad (19)$$
$n = 8$, $r = 0.660$, $r^2 = 0.436$, $s = 0.534$, $F_{1,6} = 4.64$, $p < 0.1$