Bioavailability Prediction Based on Molecular Structure for a Diverse Series of Drugs

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Received March 24, 2003; accepted August 13, 2003

Purpose. Radial basis function artificial neural networks and theoretical descriptors were used to develop a quantitative structure–pharmacokinetic relationship for structurally diverse drug compounds.

Methods. Human bioavailability values were taken from the literature and descriptors were generated from the drug structures. All models were trained with 137 compounds and tested with a further 15, after which they were evaluated for predictive ability with an additional 15 compounds.

Results. The final model possessed a 10-*31*-1 topology and training and testing correlation coefficients were 0.736 and 0.897, respectively. Predictions for independent compounds agreed well with experimental literature values, especially for compounds that were well absorbed and/or had high observed bioavailability. Important theoretical descriptors included solubility parameters, electronic descriptors, and topological indices.

Conclusions. Useful information regarding drug bioavailability was gained from drug structure alone, reducing the need for experimental methods in drug development.

KEY WORDS: RBF ANN; QSPkR; quantitative structure–property relationship; theoretical descriptors; absorption.

INTRODUCTION

The bioavailability of a drug is defined as the rate at which the drug becomes available to the body and the extent to which the dose is ultimately absorbed after administration. Strategic decisions that affect bioavailability are considerably important in drug development and may cause a delay in new drug approval. Because the majority of new drugs are intended to be administered orally, the ability of a new drug to have good bioavailability is imperative. Recent advances in lead compound identification using high-throughput and *in silico* techniques have allowed rapid identification of compounds exhibiting possible pharmacological effects, but they do not indicate concentrations of the compounds able to reach the site of action. Thus, prediction of bioavailability is an area in need of progress to aid pharmaceutical product development.

In vivo animal studies, human *ex vivo* intestinal absorption models, and cell cultures of intestinal tissues have shown to be useful predictors of human drug absorption *in vivo* (1). However, these methods are expensive, labor intensive, and require actual compound synthesis and absorption measurements to be performed.

Indeed, the bioavailability of a drug depends on a combination of factors, including dissolution, absorption, and (first-pass) metabolism. Conventional quantitative structure–pharmacokinetic relationship (QSPkR) analyses use experimentally derived properties, such as tissue:blood and octanol:buffer partition coefficients, to predict drug pharmacokinetic parameters. Experimentally obtaining this information also is time consuming and resource intensive and has proven difficult because of the complex physiological processes involved in drug pharmacokinetics and the nonlinear relationships present among drug data.

Recently, theoretical methods have been explored as a cheaper and quicker alternative. *In silico* modeling of human intestinal absorption has been performed, demonstrating the utility of this approach (2). Even though modeling overall bioavailability is substantially more complex than absorption alone, several studies have made progress in this area. One such study constructed a QSPkR for 232 commercial drugs that classified compounds into four classes of bioavailability (3). Another theoretical QSPkR for 591 compounds developed using stepwise regression (4) demonstrated that predictions were more accurate than those achieved using "Lipinski's rule of five" (5). Both studies included a broad range of chemical structures, making them substantially more valuable than models constructed simply from congeneric compounds. Prediction of bioavailability, as opposed to broad classification, was performed in the latter and not the former, whereas model testing using independent compounds was performed in the former and not the latter. To be of most use in drug development, models should ultimately be developed to predict the bioavailability of unknown compounds.

Theoretical descriptors are generated solely from the molecular structure of a compound. They are simple to calculate with the appropriate software and are gaining popularity in quantitative structure-activity relationship (QSAR) and quantitative structure–property relationship studies (6). The actual meaning of these descriptors is often unclear; hence, the relationship between theoretical descriptors and drug activity/properties is an area of increasing interest in pharmaceutical product development. The aim of the present study was to develop a QSPkR using theoretical descriptors and artificial neural network (ANN) modeling and to predict the bioavailability of a structurally diverse group of drugs.

EXPERIMENTAL

Statistica Neural Networks (StatSoft Inc., Tulsa, OK, USA) was used for building the QSPkR, and CAChe Project Leader Version 3.11 (Accelrys, Cambridge, UK), and Molecular Modeling Pro Demo 4.07 (ChemSW Inc., Fairfield, CA, USA) were used to calculate molecular descriptors from the drug structures.

The set of 167 structurally different compounds and their experimentally derived bioavailability values (%) used in this study (Table I) were collected from the literature (7–216). Where additional information regarding experimental bio-

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0724-8741/04/0100-0068/0 © 2004 Plenum Publishing Corporation

Table I. Drug and Bioavailability Data

Drug	Subset[a]	Observed (%)[a]	Target (%)[b]	Predicted ± SD (%)[c]
Acyclovir (7)	tra	15–30	23	44 ± 1.3
Alendronate (8)	tra	0.59–0.76	0.7	−6 ± 0.1
Allopurinol (9,10)	tra	30–68	49	43 ± 0.2
Amantadine (11)	tra	90	90	72 ± 0.3
Amiloride (12)	tra	50	50	37 ± 0.5
Aminoglutethimide (13)	tra	90	90	63 ± 0.1
Amiodarone (14,15)	tra	50	50	49 ± 0.5
Amitriptiline (16)	tra	30–60	45	41 ± 0.2
Amlodipine (17)	tra	60–64	62	52 ± 0.6
Amoxicillin (18)	tra	83–100	92	67 ± 0.7
Ampicillin (19)	tra	25–75	50	66 ± 0.4
Aspirin (20,21)	tra	65–71	68	81 ± 0.3
Atenolol (22)	tra	45–55	50	63 ± 0.1
Atorvastatin (23)	tra	14	14	23 ± 0.2
Atropine (24)	tra	50	50	56 ± 0.1
Azathioprine (25)	tra	80	80	66 ± 0.1
Baclofen (26)	tra	70	70	81 ± 0.4
Bendrofluazide (27)	tra	90	90	81 ± 0.1
Betamethasone (28)	tra	70	70	76 ± 0.4
Bromocriptine (29)	tra	5–10	10	25 ± 0.3
Bumetanide (30)	tra	80–100	90	78 ± 0.3
Captopril (31)	tra	60–75	68	78 ± 0.3
Carbamazepine (32)	tra	60–85	72	77 ± 0.1
Cephalexin (33)	val	81–99	90	71 ± 0.2
Chloramphenicol (34)	tra	75–90	83	80 ± 0.5
Chlordiazepoxide (35)	tra	100	100	87 ± 0.2
Chlorothiazide (36)	tra	8–20	20	43 ± 0.6
Chlortalidone (37)	tra	65–75	70	74 ± 0.3
Cimetidine (38,39)	tra	60–70	65	62 ± 0.1
Ciprofloxacin (40,41)	tra	50–70	60	66 ± 0.5
Cladribine (42)	tra	50	50	70 ± 0.6
Clindamycin (43,44)	tra	90	90	80 ± 0.7
Clodronate (45)	tra	1	1	28 ± 0.7
Clonazepam (46)	tra	95	95	103 ± 0.3
Clonidine (47)	tes	75–95	83	69 ± 0.4
Cloxacillin (48)	tra	40–50	45	76 ± 0.8
Cromoglycate (49)	tra	2–5	3	46 ± 0.1
Cyclophosphamide (50–52)	tra	>75	75	80 ± 0.2
Cytarabine (53)	tra	20	20	29 ± 0.9
Dexamethasone (54)	tra	80–90	90	79 ± 0.2
Diazepam (55)	tra	85–100	93	76 ± 0.1
Dicloxacillin (56)	tra	35–76	56	75 ± 0.7
Didanosine (57,58)	tra	40–50	45	74 ± 0.1
Disopyramide (59)	tra	72–94	83	70 ± 0.1
Dolasetron (60)	val	90	90	62 ± 0.3
Domperidone (61)	tra	15–17	16	54 ± 0.5
Doxapram (62)	tra	60	60	46 ± 0.2
Doxepin (63)	tes	30	30	53 ± 0.2
Doxorubicin (64)	tes	<5	5	29 ± 0.1
Doxycycline (65)	tra	93	93	65 ± 0.2
Enalapril (66–68)	tra	50–70	60	51 ± 0.7
Ethambutol (69)	tra	69–85	77	66 ± 0.7
Ethinyloestradiol (70)	tra	40–50	45	24 ± 0.0
Etoposide (71)	tra	45–50	48	23 ± 0.0
Etidronate (72)	tra	5	5	17 ± 0.2
Famotidine (73)	tra	40–50	45	47 ± 0.8
Felodipine (74)	tes	20	20	53 ± 0.6
Fexofenadine (75)	tra	30	30	30 ± 1.1
Finasteride (76)	tra	80	80	62 ± 0.1
Flecainide (77)	tra	85–90	88	64 ± 0.3
Fluconazole (78)	tra	>90	90	80 ± 0.2
Flucytozine (79)	tra	75–89	82	71 ± 0.3

Table I. Continued

Drug	Subset[a]	Observed (%)[a]	Target (%)[b]	Predicted ± SD (%)[c]
Flunitrazepam (80)	tra	90	90	102 ± 0.4
Fluorouracil (81)	tra	30	30	77 ± 0.2
Fluvastatin (82)	tra	24–24	24	51 ± 0.2
Furosemide (83–85)	tra	60–67	64	82 ± 0.5
Gabapentin (86)	tra	50–70	60	72 ± 0.2
Gemfibrozil (87)	tra	90	90	62 ± 0.3
Glibenclamide (88,89)	tra	80	80	47 ± 0.5
Glipizide (90–92)	tra	90	90	58 ± 0.9
Haloperidol (93)	tra	70	70	76 ± 0.2
Hydralazine (94)	tes	30–50	40	57 ± 0.5
Hydrochlorthiazide (95)	val	60–80	70	44 ± 0.6
Ibuprofen (96)	tra	85–100	93	76 ± 0.3
Idarubicin (97,98)	val	20–30	25	44 ± 0.5
Imipramine (99)	tra	26–68	47	40 ± 0.1
Indapamide (100)	tes	90–100	90	95 ± 0.3
Indomethacin (101,102)	tra	98	98	80 ± 0.4
Irbesartan (103)	tra	60–80	70	61 ± 0.8
Isosorbide dinitrate (104,105)	tra	25	25	28 ± 0.7
Isosorbide mononitrate (106)	tra	80–100	90	58 ± 0.1
Ketamine (107)	tra	20	20	53 ± 0.7
Ketoprofen (108)	tra	90–100	95	89 ± 0.4
Labetalol (109,110)	val	30	30	71 ± 0.6
Lamivudine (111,112)	tra	66–87	77	61 ± 0.3
Lamotrigine (113,114)	val	95	95	77 ± 0.1
Lansoprazole (115,116)	tra	80–90	85	80 ± 0.3
Levodopa (117)	tra	44	44	61 ± 0.4
Lidocaine (118)	tra	24–46	35	61 ± 0.5
Lisinopril (119)	tes	40	40	55 ± 0.3
Lithium carbonate (120)	tra	100	100	84 ± 0.6
Loperamide (100)	tra	<40	40	35 ± 0.4
Lorazepam (121)	tes	95	95	94 ± 0.4
Losartan (122)	val	33	33	40 ± 0.4
Meperidine (123)	tes	50–60	55	52 ± 0.7
Mercaptopurine (124–126)	tra	16–46	31	42 ± 0.6
Metformin (127)	tra	50–60	55	70 ± 0.4
Methotrexate (128)	tra	60–75	68	48 ± 0.1
Methyldopa (129)	val	60–70	65	61 ± 0.3
Methylprednisolone (130)	tes	79–82	81	71 ± 0.5
Metoclopramide (131)	val	30–90	60	70 ± 0.3
Metoprolol (132)	tra	50–50	50	59 ± 0.1
Metronidazole (133)	tra	90	90	82 ± 0.8
Mexilitine (134)	tra	80–100	90	70 ± 0.4
Mianserin (135)	tra	30	30	32 ± 0.1
Minocycline (136)	tra	100	100	74 ± 0.3
Misoprostol (137)	tra	80	80	69 ± 0.2
Morphine (138–141)	tra	20–33	27	28 ± 0.2
Naloxone (142)	val	2–10	6	42 ± 0.2
Naltrexone (143)	val	20–22	20	38 ± 0.7
Nifedipine (144)	val	45–85	65	62 ± 0.1
Nimodipine (145)	tra	13	13	59 ± 0.2
Nitrazepam (146)	tra	80	80	101 ± 0.5
Nizatidine (147,148)	tra	90	90	71 ± 0.2
Norfloxacin (149)	tra	45	45	79 ± 0.1
Nortriptyline (150–152)	tra	46–56	51	44 ± 0.0
Omeprazole (153,154)	tra	40–60	50	71 ± 0.8
Ondansetron (155–158)	tra	48–75	62	60 ± 0.7
Orciprenaline (100)	tra	40	40	76 ± 0.5
Oxprenolol (159)	tra	50	50	58 ± 0.1
Oxycodone (160)	tra	50	50	31 ± 0.1
Pamidronate (161)	tra	1	1	–3 ± 0.1
Pantoprazole (162)	tes	80–97	89	75 ± 0.2
Paracetamol (163)	val	58–68	63	77 ± 0.2
Pethidine (164)	tra	60	60	57 ± 0.6

Table I. Continued

Drug	Subset[a]	Observed (%)[a]	Target (%)[b]	Predicted ± SD (%)[c]
Phenobarbitone (100)	tra	70–90	80	69 ± 0.3
Phenytoin (165)	tra	98	98	74 ± 0.1
Pindolol (166)	tra	90	90	63 ± 0.5
Pravastatin (167)	tra	17–34	26	67 ± 0.6
Prazosin (168–170)	tra	43–82	63	67 ± 0.3
Primidone (171,172)	tra	60–80	70	68 ± 0.2
Procainamide (173)	tra	67–99	83	78 ± 0.1
Prochlorperazine (174)	tra	20	20	44 ± 0.7
Promethazine (175)	tes	25	25	38 ± 0.2
Propranolol (176)	tra	26–46	36	68 ± 0.1
Propylthiouracil (177)	val	80–90	85	88 ± 0.3
Quinapril (178)	tra	50–60	55	39 ± 0.0
Quinidine (179)	tes	54–88	70	67 ± 0.2
Ramipril (180)	tra	50–60	55	57 ± 0.3
Ranitidine (181)	val	40–80	60	75 ± 0.2
Ribavirin (182)	tra	40–64	52	45 ± 0.5
Salicyclic acid (183)	tra	100	100	79 ± 0.2
Selegiline (184,185)	tra	20	20	0 ± 0.2
Simvastatin (186)	tra	5	5	8 ± 0.4
Sotalol (187,188)	tra	95	95	81 ± 0.4
Spironolactone (189)	tra	70–90	80	87 ± 0.1
Sulfamethoxazole (190)	tra	80–90	85	69 ± 0.4
Sulfisoxazole (191)	tra	100	100	73 ± 0.4
Sumatriptan (192,193)	tra	15–20	18	71 ± 0.7
Tacrine (194)	tra	30–40	35	51 ± 0.4
Temazepam (195,196)	tra	90	90	91 ± 0.3
Terbutaline (197)	tra	15	15	46 ± 0.7
Testosterone (198)	tra	5	5	45 ± 0.2
Tetracycline (199,200)	tes	77	77	72 ± 0.7
Theophyline (201)	tra	80–100	90	76 ± 0.8
Thioprofenic acid (202)	tra	100	100	81 ± 0.1
Timolol (203)	tra	30–50	90	79 ± 0.1
Tolbutamide (204)	tes	93	93	69 ± 0.5
Triamterene (205–207)	tra	50	50	55 ± 0.1
Trimethoprim (208,209)	tra	90–97	94	61 ± 0.2
Trimipramine (210)	tra	40	40	39 ± 0.0
Tropisetron (211)	tra	60	60	59 ± 0.2
Valproic acid (212)	tra	95–100	100	87 ± 0.7
Verapamil (213)	tra	20–35	28	39 ± 0.3
Warfarin (214)	tra	98	98	94 ± 0.3
Zalcitabine (215)	tra	70–88	79	58 ± 0.1
Zidovudine (216)	tra	60–65	63	49 ± 0.4

[a] tra, training set; tes, testing set; val, validation set.
[b] Bioavailability values from literature.
[c] Target bioavailability values used for models.
[d] Bioavailability predicted by ANN.

availability was required, values from more than one reference were sought. Before training, the data were divided randomly into three separate subsets: training (137 compounds), testing (15 compounds), and validation (15 compounds). Bioavailability values for the test and validation subsets thus divided were examined statistically to ensure adequate representation of the training set ($p = 0.91$).

Each of the 167 drug molecules was presented in mol format, which describes compounds as a connection table with the three-dimensional coordinates of all atoms. From the mol files, 76 theoretical descriptors (217–232) were generated (Table II) that aimed to numerically encode meaningful features of each molecule. A three-layered radial basis function (RBF) ANN containing a bias neuron in each layer and a single neuron in the output layer was used. The calculated molecular descriptors were used as inputs to the ANN and the target output was the bioavailability data. Network weights and biases were initialized with random values before each training run, and all runs were performed in replicates of five. The training set was used to train the ANN, the testing set to evaluate ANN performance and monitor overtraining, and the validation set to evaluate the predictive ability of the trained model. Training was stopped when the training root mean squared (RMS) error failed to improve over a given number of training cycles and when the testing RMS error started to increase. The training and testing correlation coeffi-

Table II. Calculated Structural Descriptors

Constitutional descriptors	Chemical composition (weight percent of C, H, O, N, S, Cl, F in molecular mass), atom count (C, H, N, S, Cl, F, S, O), functional group counts (amine, aldehyde, amide, carbonyl, carboxylate, cyano, ether, hydroxyl, methyl, methylene, nitro, nitroso, sulfide, sulfone, sulfoxide and thio)
Topological descriptors	Randic connectivity indices (217) ($^0\chi$–$^4\chi$), valence connectivity indices (218) ($^0\chi^v$–$^4\chi^v$), Kier's topological shape indices (κ^1–κ^3) (219), difference indices ($^0\Delta$–$^4\Delta$), (220), 3-D Weiner number (221), chemically intuitive molecular indices (eigenvalue 1–14) (222)
Chemical descriptors	Molecular mass, parachor, surface tension, polarizability, density, *pK*a, *pK*a^0, logP, logD
Geometrical descriptors	Solvent accessible surface, molar volume
Quantum chemical descriptors	Dipole moment, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies, dielectric energy, steric energy, heat of formation, total energy, minimum energy, electron affinity
Bulk Properties	Molecular weight, Van der Waals volume, surface area, molecular volume (223), molar volume (224), density, molecular length, width and depth
Solubility Parameters	Octanol-water partition coefficient (fragment addition (225) and atom based (226) log P), molar refractivity (MR), Q log P (227), hydrogen bonding number, van Krevelen and Hansen's solubility and 3D solubility parameters (dispersion, polarity and hydrogen bonding), mean water of hydration (228), hydrophilic-lipophilic balance (molecular weight and volumetric HLB), hydrophilic surface area and % hydrophilic surface area, polar surface area (229), surface tension, water solubility (230) (logW – log water solubility, g/L), log molar water solubility (log Kow), water solubility estimated from log Kow (log Sw) (231), log molar olive oil – gas partition coefficient (232)

cients (r_{train} and r_{test} respectively) were used to evaluate the overall quality of a particular subset of descriptors and the corresponding network topology.

Input Variable Selection

Both manual and automatic pruning techniques were used to reduce the number of input variables. Sensitivity analysis of inputs was used to identify significance of individual molecular descriptors and to select descriptors that were considered the most important. The sensitivity value for each descriptor was calculated in the following manner: information contained in the descriptor was substituted with meaningless values and the network was retrained. The error associated with the retrained network was then compared with the baseline error of the optimum model. Sensitivity of the descriptor was defined as the ratio of the former to the latter. Hence, sensitivities greater than one indicated that the descriptor provided useful information and removal of that descriptor would be detrimental to the model. Higher sensitivities correspond to a greater reliance of the ANN on the information content of the corresponding descriptor. Based on results of sensitivity analyses, inputs with sensitivities less than one were eliminated sequentially from the model. As the number of input variables was reduced, descriptors with sensitivity greater than one but low relative values were removed manually. Activations can be either positive or negative and represent the strength of the output from a given neuron. High absolute activations indicate a substantial contribution to the model and low absolute activations indicate the opposite. Input neurons displaying a zero activation do not contribute to the system at all, and these were manually pruned from the model. The ANN program also used regularization and search algorithms for automatic descriptor selection.

Network Design

RBF ANNs have only a single hidden layer of radial neurons, which use a Gaussian transfer function. All 76 descriptors were included in the initial model after which pruning was implemented. Repeated training runs for each configuration were necessary to avoid undertraining and also to prevent the network from falling into local minima. If the network was undertrained and did not achieve an acceptable performance level, the model was discarded and another replicate was performed.

Predictive network performance was evaluated according to an efficiency ratio (ER) defined as the ratio of the validation correlation coefficient (r_{val}) to the training correlation coefficient:

$$\mathrm{ER} = r_{val}/r_{train}$$

The validation coefficient of correlation is generally lower than training, such that the efficiency for prediction of a validation data set is lower than for prediction of the training set. Because training indicates how well the ANN manages the given data and validation is indicative of predictive performance, then ER represents how efficient the ANN is at generalizing.

RESULTS AND DISCUSSION

The first step in developing the QSPkR was to calculate the numerical descriptors. Structural features including bulk properties, solubility parameters, constitutional, chemical, geometrical, quantum chemical, and topological descriptors were generated for each drug molecule. The next step was to refine the model by variable selection or pruning (233). This caused a reduction in the size and complexity of the model, shortened training time, and improved network performance. Initially, a neural network consisting of 76 input variables, one hidden layer, and one output neuron for the target bioavailability was used. After pruning, the number of inputs was reduced from 76 to 66, 47, 27, 24, 19, 12, 10, 9, 7, and finally to 4 inputs. ER increased as descriptors were removed and peaked at the 47 input model after which it began to decrease (Table III). A second peak was seen for the 10 input model and further pruning caused a decrease in ER.

The ANN model with 10 input descriptors and 31 hidden neurons was found to have the highest r_{test} value and a high ER. Other architectures containing different numbers of hid-

Table III. Model Summary

Model	ER	r_{train} ± SD	r_{test} ± SD	r_{val} ± SD
79-*29*-1	0.52	0.668 ± 0.000	0.801 ± 0.003	0.349 ± 0.008
66-*18*-1	0.58	0.629 ± 0.002	0.782 ± 0.001	0.365 ± 0.020
47-*20*-1	1.11	0.608 ± 0.004	0.771 ± 0.004	0.678 ± 0.009
27-*28*-1	1.00	0.688 ± 0.001	0.845 ± 0.002	0.686 ± 0.005
24-*31*-1	0.88	0.702 ± 0.002	0.850 ± 0.001	0.620 ± 0.007
19-*44*-1	0.71	0.721 ± 0.004	0.865 ± 0.010	0.509 ± 0.021
12-*54*-1	0.45	0.779 ± 0.005	0.887 ± 0.000	0.354 ± 0.003
10-*31*-1	0.92	0.736 ± 0.000	0.897 ± 0.004	0.680 ± 0.002
9-*44*-1	0.73	0.760 ± 0.002	0.834 ± 0.002	0.552 ± 0.004
7-*37*-1	0.70	0.732 ± 0.000	0.870 ± 0.007	0.513 ± 0.002
4-*8*-1	0.76	0.469 ± 0.004	0.547 ± 0.011	0.354 ± 0.017

den neurons were examined but they produced poorer quality neural network models and worse predictions. Since the 10 input model achieved relatively high r_{val} and ER values, it was taken as the optimum model and subjected to further analysis.

Statistical Analysis

Because the variance of experimental bioavailability values between subsets was not significant ($p > 0.7$) and normality for all subsets was able to be assumed ($p > 0.10$), a high analysis of variance statistic indicated that compounds selected in the testing and validation subsets were representative of the training set (Table IV). Statistical analysis of the descriptor data was not performed before pruning because removal of a large number of descriptors would greatly change the apparent descriptor space. However, analysis of the optimum descriptor set was performed and revealed low differences in variance between subsets ($0.15 < p < 0.80$) and mostly normal distributions. Appropriate parametric and nonparametric analyses of individual descriptors did not reveal any significant differences between information contained in training, testing or validation subsets ($0.15 < p < 0.97$). A Bonferroni post-hoc analysis revealed similar results (data not shown).

Descriptor Analysis

Because of uncertainty in the weight matrices of conventional back-propagation ANNs, conclusions about relationships between input and output variables are difficult to make. Use of RBF ANNs, however, does allow these relationships to be examined (234). The 10 descriptors in the optimum model and their overall sensitivity ranks, defined as the average of training and testing sensitivity values, are given in Table IV. Sensitivity ratios varied slightly between training and testing sets (Fig. 1) although relative values and, hence, sensitivity ranks were not considerably affected. The optimum model indicated that physicochemical factors affect drug absorption and consequently bioavailability including the intrinsic solubility (PSA) of the drug molecule, as well as its electronic nature (electron affinity, dielectric and conformational energy, aromatic ring counts), and molecular size and shape characteristics (molar refractivity [MR], and connectivity, difference and shape indices). Each of the descriptors in the optimum model had different effects on the predicted bioavailability (Fig. 2). The response graphs were generated by varying the values of the descriptor in question while holding values for all the other descriptors constant. They displayed the effect of each descriptor on the predicted bioavailability.

It has been shown that polar surface area (PSA) with hydrogen bonding capacity (PSA and the presence of –OH groups) plays a significant role in the description of drug membrane penetration (235), and that PSA can be used as a predictor of absorption (236). Molecular surface area and volume are highly correlated geometrical descriptors that can provide information about contact surface, surface diffusion, absorption and information of the size of the molecules. The contact surface area can be viewed as an indicator of the extent to which the solute is exposed to intermolecular interaction with the solvent (237) and has been used as an accurate predictor of water solubility (238). Drugs need to be in solution before they can be absorbed from the gastrointestinal tract. Therefore, as a general rule, a drug that is very poorly soluble or insoluble in water would have variable or unreliable absorption.

Table IV. Significance Values for Statistical Tests and Input Sensitivity Ranks

Data	Input symbol	Training normality[a]	Testing normality[b]	Validation normality[b]	Variance[c]	ANOVA[d]	Sensitivity rank
Bioavailability	—	0.11	0.12	0.32	0.74	0.91	—
Difference index $^2\Delta$	Ar.ring	0.03	0.06	0.23	0.66	0.71	2
Kappa shape index κ^2	Conform	0.10	0.35	0.03	0.48	0.83	7
Aromatic ring counts	Conn1	>0.01	0.05	0.01	0.70	0.62[e]	6
Molar refractivity	Dielec	0.20	0.98	0.31	0.22	0.50	3
Dielectric energy	Diff2	>0.01	0.01	0.04	0.18	0.17[e]	8
Electron affinity	El.aff	>0.01	0.08	0.40	0.76	0.57	5
Conformation minimum energy	Kappa2	0.20	0.66	0.94	0.80	0.97	10
Polar surface area	MR	0.20	0.24	0.36	0.16	0.71	9
Connectivity index $^1\chi$	PSA	0.20	0.89	0.55	0.71	0.55	1
Valence connectivity index $^4\chi^v$	Val4	0.15	0.44	0.59	0.75	0.53	4

[a] Kolmogorov-Smirnov test of normality.
[b] Shapiro-Wilk test of normality.
[c] Levene's homogeneity of variance.
[d] Analysis of variance (ANOVA) except where indicated.
[e] Kruskal–Wallis test.

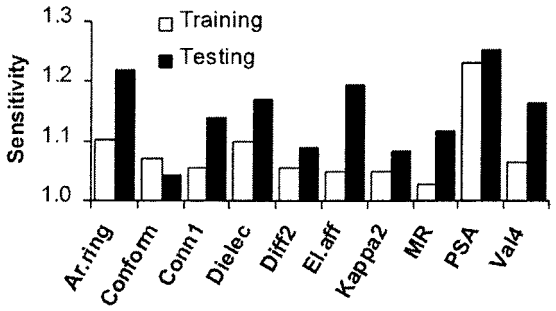

Fig. 1. Training (open columns) and testing (filled columns) sensitivities for optimum model.

PSA also indicates the capacity of a compound to form hydrogen bonds. Hydrogen bonds are major forces of recognition in biochemistry and molecular pharmacology: they are an essential component of intermolecular interactions. Calculated surface characteristics of molecules have been correlated with a number of physicochemical properties of drug molecules including lipophilicity, the energy of hydration and the hydrogen bond formation capacity (239,240). An increase in the value of PSA in the optimum model corresponded to an initial positive effect on bioavailability but then caused predicted bioavailability to drop substantially (Fig. 2i).

A dielectric material is a substance that is a poor conductor of electricity, but an efficient supporter of electrostatic fields. All molecules have surfaces, and charge can accumulate on those surfaces. Charge accumulation can affect the formation of hydrogen bonds, which has been shown to play an important role in enzymatic catalysis (241). The strength of hydrogen bonds between an enzyme and substrate changes over the course of a reaction. The binding energy of an enzyme is used to fix the substrate in the low-dielectric active site, from where the strength of the hydrogen bond is increased over the course of a reaction. The dielectric energy descriptor accounts for the original charge arrangement on the surface of the molecule, and thus would be indicative of the metabolic susceptibility of a drug molecule. The effect of increasing the dielectric energy in the optimum model was to reduce predicted bioavailability for most of the range (Fig. 2d). Higher dielectric energies corresponded to negatively predicted bioavailability values; however, negative bioavailability is not possible in a physiologic sense. The explanation is that the final predicted bioavailability is a combination of the influence of all the descriptors and not a product of only one. Therefore, the response graphs do not indicate the absolute value of the predicted bioavailability based on a particular descriptor but instead indicate the influence of that descriptor on bioavailability.

For a drug to be absorbed from the gastrointestinal tract (GI) tract, it must be capable of moving across cell membranes (transcellular absorption) or between the tight gaps that are formed between cells (paracellular absorption). Drug penetration through the biologic membranes depends upon a number of molecular properties, such as lipophilicity, polarity, degree of ionization and molecular size. Penetration between the cell gaps depends on molecular size and the concentration gradient. Molecular size, in general, limits the absorption of drugs through membranes. Small, lipid-insoluble substances penetrate cell membranes via the pores between aqueous phases on both sides of the membrane. The rate of

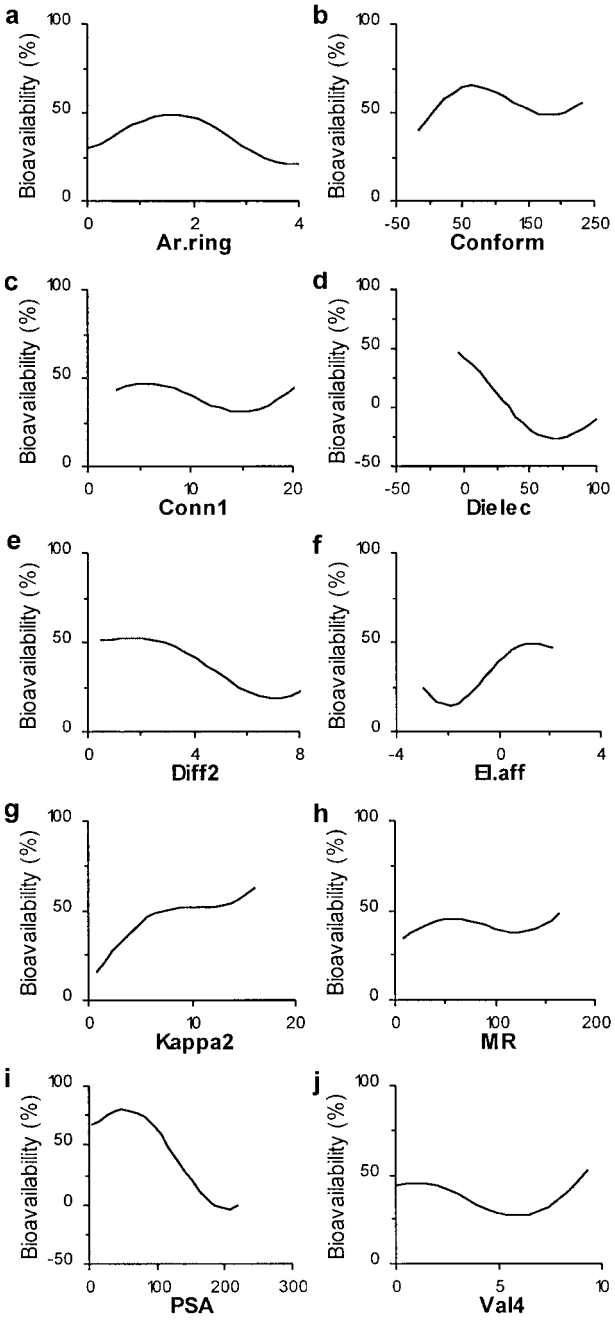

Fig. 2. Response graphs for optimum descriptor set.

such passive diffusion depends on the size of the pores, the molecular volume of the solute, and the solute concentration gradient. Compounds with low molecular mass (242) that are not ionized and are lipophilic will have higher bioavailability simply because diffusion through pores is much easier. Calculation of MR is based upon both molar mass and density, and MR has been shown to be correlated with geometric volume (243). Geometric volume relates to molecular size, indicating that MR would contribute to the observed absorption of drugs from the GI tract. The relationship between MR and bioavailability appeared to follow a cubic trend (Fig. 2h). Hence, increasing MR caused predicted bioavailability to initially increase, decrease, then increase again. This demon-

strated the nonlinearity apparent between the descriptor and target output spaces.

Over the last 10 years, a variety of topologic and shape descriptors for characterization of molecular structure in combination with molecular dynamic analysis have emerged as alternative descriptors in quantitative structure-activity studies (244). The advantage of these descriptors is that they can be calculated for any chemical structure, real or hypothetical. Molecular connectivity indices represent molecular structure in a manner similar to the counts of carbon atoms, but in much more general way. That is, χ indices are weighted counts of structure features with the same mathematical qualities as counts, but with much more structural information. Structural features such as size, branching, unsaturation, heteroatom content and cyclicity are encoded. The connectivity approach is fundamentally different from traditional biological QSAR methods based on assumed mechanisms and using physicochemical properties as regression variables. The connectivity method directly correlates structural information with molecular activity and not indirectly through an intermediate physical property. The structure base of χ indices has enabled sufficient information to be extracted from QSAR equations to allow molecules to be designed directly from those equations (245). Connectivity indices up to the fourth order are known to encode various molecular properties including molecular density, branching and aromatic ring substitutions. Linear combinations of connectivity indices have been useful, especially in dealing with structurally diverse data sets (220). In addition to encoding structural information, the difference index $^2\Delta$ also provides information on inductive and delocalization effects. Even though there were slight positive gradients of the response at the extremes of the graph, there was an overall negative trend in the response of bioavailability to the $^2\Delta$ descriptor (Fig. 2e).

The first order connectivity index, $^1\chi$ encodes single bond properties and is a weighted count of bonds, being related to the types and position of branching in the molecule. $^2\chi$ also provides information about the types and position of branching and may indicate the amount of structural flexibility of a molecule. Although it is derived from fragments of two bond lengths, $^2\chi$ is highly correlated with $^1\chi$. Structural and steric information contained in $^1\chi$ is also reflected in other descriptors related to molecular shape.

The three topological shape indices (219) numerically quantify molecular topology. They present information concerning the size, shape, branching pattern, cyclicity and similarity of molecular graphs. κ^2 encodes linearity of a molecule, and inclusion in the current model for bioavailability would provide structural and shape information not present in $^1\chi$.

Valence connectivity indices (246) use the same graph invariant as the χ indices described previously, but with modified vertex degrees to account for heteroatoms. Practical application of χ indices is heavily dependent upon the ability to deal with molecules containing heteroatoms. Valence connectivity indices are calculated using the number of valence electrons in the corresponding atom, and can be used to differentiate between heteroatoms in various functional groups. $^4\chi^v$ accounts for heteroatom substitution on benzene rings, the aromatic nature of which can affect solubility of a compound.

The response graphs for $^1\chi$ (Fig. 2c), κ^2 (Fig. 2g), and $^4\chi^v$ (Fig. 2j) all display nonlinear relationships with bioavailability. The overall influences of $^1\chi$ and $^4\chi^v$ were similar in appearance perhaps reflecting their common origin. The more pronounced effect of $^4\chi^v$ was expected since $^4\chi^v$ is a more complex descriptor than $^1\chi$.

Although molecular solubility descriptors and topological shape indices can successfully rationalize compound solubility, they do not provide information on electronic influence through bonds or across space. Electronic properties, such as field and resonance effects, may play a role in describing the magnitude of biological activity in conjunction with structural features encoded in indexes. This can be explained by the fact that electron affinity was included in the model as a physical property that influences the chemical behavior of the molecule. Electron affinity is the change in the total energy of a molecule when an electron is added to form a negatively charged ion. For drugs that can ionize, solubility will depend on physiological factors such as the local pH conditions within the stomach and intestines. Resonance effects are influenced by the presence of aromatic rings. When a hydroxyl group is appended to an aromatic ring, the resultant phenol is a weak acid and is able to dissociate in water to form the corresponding phenolate anion. This dissociation is more facile due to resonance stabilization of the phenolate, in which the negative charge delocalizes into the aromatic system. Such charge delocalization causes a decrease in the electron density of the group attached to aromatic ring and an increase in the electron density of the aromatic ring itself. Aromatic compounds are characterized by a special stability and they undergo substitution reaction more easily that addition reaction. Inclusion of aromatic ring counts in the final model would also complement the information provide by $^4\chi^v$. Quantum chemical descriptors further describe electronic and reactive properties of drug molecules. Minimum energy of a molecule is indicative of stability and reactivity. Increasing reactivity of a molecule corresponds to an increased potential for metabolism, which would then affect drug bioavailability.

The response graphs for aromatic ring counts (Fig. 2a) and conformational minimum energy (Fig. 2b) presented nonlinear relationships with bioavailability. The influence of aromaticity appeared to be roughly inversely parabolic. Hence, increasing the number of aromatic rings increased bioavailability to a maximum after which there was negative effect on bioavailability. Although the effect of aromaticity appeared inversely parabolic, such a conclusion is only true for a compound containing up to four aromatic rings. In fact there seemed to be a point of inflexion when there were three aromatic rings present. If the number of aromatic rings was greater than four then the proposed parabolic relationship may instead be similar to the relationship displayed for conformational minimum energy (Fig. 2b). This nonlinearity in the relationship between descriptors and the target bioavailability necessitates any model to be trained on as broad a range of chemical structures as possible. The training set of compounds should adequately represent the chemical space of the test compounds to avoid the problem of extrapolation.

Model Performance

The training, testing, and validation RMS errors for the optimum model with 10 descriptors were 19.21, 16.15, and 20.47, respectively. The strength of the correlation between selected descriptors and bioavailability corresponds to the quality of prediction. For training and test subsets, correla-

tions between predicted and observed values of 0.736 and 0.897, respectively, were achieved. These correlations further indicate that low predicted values correspond to the low observed bioavailability, and high predictions to high observed bioavailability values (Fig. 3).

For both training and validation subsets, more accurate predictions were made for compounds with observed bioavailability greater than 50%. Low bioavailability is most common with poorly water-soluble, slowly absorbed drugs. More factors affect bioavailability when absorption is slow or incomplete than when it is rapid and complete, hence, slow or incomplete absorption often leads to variable therapeutic responses. Many drugs have low oral bioavailability as a result of extensive first-pass metabolism.

Higher bioavailability values were predicted for the mainly basic drugs acyclovir, chlorothiazide, cromoglycate, domperidone, felodipine, fluorouracil, nimodipine, and sumatriptan. Bioavailability of acyclovir is dose dependent: absorption, and thus bioavailability, decreases with increasing dose, the nonlinearity of which may be difficult to account for in any model.

Negative bioavailabilities were predicted for alendronate, pamidronate, and selegiline during training. Since bioavailability can only take positive values then it is safe to assume that a negative prediction suggests extremely low clinical bioavailability. This observation is consistent with literature bioavailability of alendronate and pamidronate which both have reported values of 1% or less. Oral doses of selegiline are heavily metabolized on first-pass through the liver, and the active metabolites amphetamine and methamphetamine are produced. It is unclear whether clinical antidepressant effects observed after oral administration are the result of MAO-A inhibition by selegiline or the actions of amphetamine and methamphetamine. Clinical effect is dependent upon bioavailability so the low predicted value for selegiline might indicate a greater role of the active metabolites in producing the clinical effects seen with selegiline.

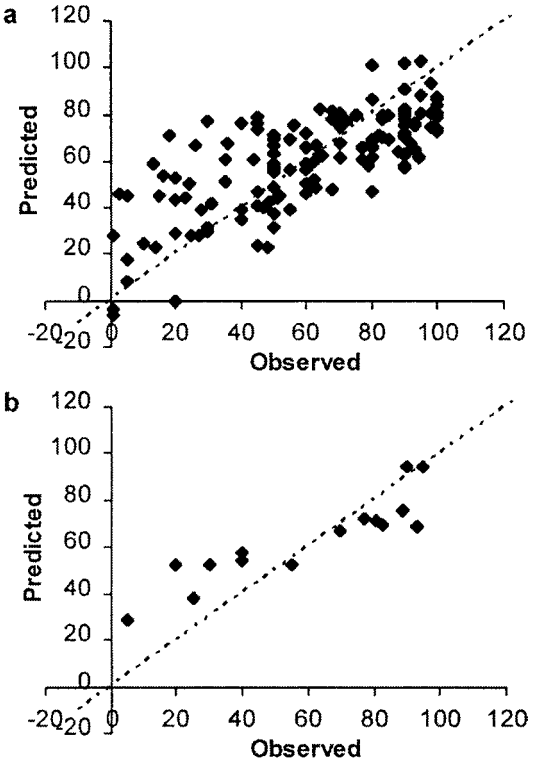

Fig. 3. Optimum model predicted bioavailability (%) values for (a) training set and (b) test set.

Independent Predictions

Predicted values for the independent validation set are shown in Fig. 4 in ascending order of observed bioavailability. Where data ranges for experimental bioavailability were given in the literature, error bars were included to denote the range. Error bars were not included on predicted values because variations in intra-drug predictions were negligible. Again, more accurate predictions were made for compounds exhibiting higher experimental bioavailabilities such as cephalexin, lamotrigine, methyldopa, metoclopramide, nifedipine, paracetamol, propylthiouracil, and ranitidine. Predicted bioavailability for dolasetron correctly indicated that values were relatively high, and low bioavailability for losartan was correctly predicted.

Idarubicin, labetalol and naltrexone are all well absorbed rapidly after oral administration. Labetalol is extensively metabolized by the liver, and possibly in the gut wall, to *O*-phenyl-glucuronide, *N*-glucuronide, and a glucuronide formed by conjugation at the secondary alcohol group. Once idarubicin is absorbed, it disappears rapidly from the blood and is distributed throughout the entire body. It shows a rapid distributive phase with a very high volume of distribution presumably reflecting extensive tissue binding. Naltrexone is subject to first-pass metabolism resulting in naltrexol and conjugated naltrexone and naltrexol as the major metabolites. Bioavailability of naltrexone varies greatly due to its substantial hepatic metabolism, with different studies reporting values between 5–22% (247,248).

Hydrochlorothiazide is absorbed throughout the small intestine and is not metabolized but is eliminated rapidly by the kidney with over 60% eliminated unchanged in the urine. Although relatively high, experimental bioavailability values span a large range, which may explain the lower than expected predicted bioavailability for hydrochlorothiazide.

Overall, predictions were in good agreement with observed values for drugs exhibiting higher bioavailability. Sys-

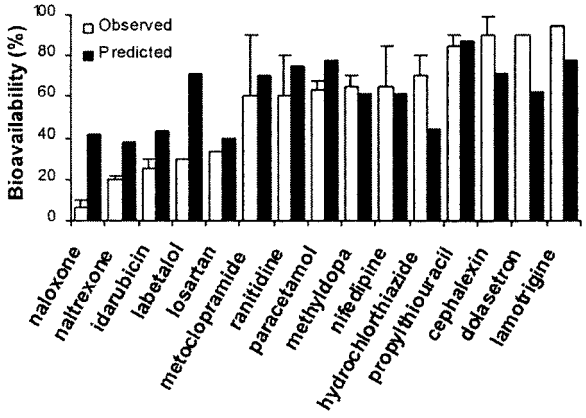

Fig. 4. Optimum model predicted SD < 0.70 vs. observed values for validation set.

temic bioavailability is a combination of absorption and metabolism of orally administered drugs. Compounds with high bioavailability would generally be well absorbed through the GI tract and not overly prone to first-pass metabolism either in the gut or by the liver. Compounds with lower bioavailability would either be poorly absorbed from the GI tract or substantially metabolized prior to becoming systemically available. Many physicochemical factors influence metabolic susceptibility of the compounds themselves, in addition to genetic and physiologic characteristics of the human subjects. Enzymatic metabolism is a complex and diverse range of processes so compounds with poor bioavailability in the current study may not have been predicted well because of this complexity. It is well known that all the information in an ANN model is contained in the weights connecting the neurons. Some researchers suggest that the ideal ratio of the number of training patterns to the number of connection weights, or ρ parameter, lies within the range $1.8 < \rho < 2.2$. The claim is that ANN models with values of ρ above this range may have insufficient connections to encode meaningful information, and models with values of ρ below this range would have too many connections and training data would then become memorized. Although the optimum model in the current study had a ρ value around 0.4, it has been shown that ideal ρ is implementation dependant and relies on the nature of the training data itself (249). Furthermore, the current study made use of both a test set of compounds to examine model training, as well as an independent validation set to examine predictive ability. Utilization of data in such a manner would virtually eliminate possible effects of memorization. The optimum predictive model was constructed with 31 neurons in the hidden layer. The necessity of having such a large number of neurons and, hence, a large number of connections indicated the inherent difficulty in modeling bioavailability.

The optimum model in the current study predicted higher than observed bioavailability values for a number of compounds in the validation set, all of which were reported to be well absorbed following oral dosing. Thus, for screening purposes the current model may be suitable for compounds that have been shown to be absorbed well from the GI tract. Alternatively, since for the most part compounds were correctly predicted as having either higher (greater than 50%) or lower (less than 50%) bioavailability, the model may be useful for differentiating between compounds with either low or high bioavailability.

CONCLUSION

The QSPkR model described in the current study did not require experimental parameters but relied on theoretical information generated from drug structure. A structurally diverse data set was used and the models developed were tested with both internal and independent external validation compounds. Successful predictions were made for compounds exhibiting high bioavailability, as well as compounds with poor bioavailability but good absorption.

The descriptors remaining in the optimum model could potentially provide useful information regarding structural properties required to develop compounds with adequate bioavailability characteristics. Alternatively, the data presented may be used for the preliminary evaluation of the bioavailability of potential drug candidates without performing expensive laboratory experiments to accomplish the same feat. Since the cost of drug development is many times larger than the cost of drug discovery, predictive methodologies aiding in the selection of drug candidates with suitable bioavailability characteristics are of considerable significance.

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