4844 J. Med. Chem. 2009, 52, 4844–4852
DOI: 10.1021/jm900403j

Journal of Medicinal Chemistry Article

Physicochemical Determinants of Human Renal Clearance

Manthena V. S. Varma,* Bo Feng, R. Scott Obach, Matthew D. Troutman, Jonathan Chupka, Howard R. Miller, and Ayman El-Kattan

Pharmacokinetics Dynamics and Metabolism, Pfizer Global Research and Development, Pfizer Inc., Groton, Connecticut

Received March 30, 2009

Kidney plays an important role in the elimination of drugs, especially with low or negligible hepatic clearance. An analysis of the interrelation of physicochemical properties and the human renal clearance for a data set of 391 drugs or compounds tested in humans is presented. The data set indicated that lipophilicity shows a negative relationship while polar descriptors show a positive relationship with renal clearance. Analysis of net secreted and net reabsorbed subsets revealed that hydrophilic ionized compounds are probable compounds to show net secretion and a possible drug−drug interaction due to their likely interaction with uptake transporters and inherent low passive reabsorption. The physicochemical space and renal clearance were also statistically analyzed by therapeutic area. In conclusion, ionization state, lipophilicity, and polar descriptors are found to be the physicochemical determinants of renal clearance. These fundamental properties can be valuable in early prediction of human renal clearance and can aid the chemist in structural modifications to optimize drug disposition.

Introduction

The pharmacokinetic profile of a drug molecule is a complex function of various serial and/or simultaneous processes that include dissolution, intestinal absorption, plasma protein binding, metabolic clearance, body distribution, and renal and other clearance mechanisms. Thus, the ability to predict absorption, distribution, metabolism, and elimination for virtual compounds and new chemical entities is highly valuable in drug discovery and development. The excretion of unchanged drugs by the kidneys constitutes one of the major routes of drug elimination, particularly for the drugs with low or negligible metabolic and biliary clearances.[1,2] Renal clearance is also very important for metabolites of drugs, as exemplified by the excretion of drug-related material in urine during radiolabel mass balance−excretion studies in humans.[3]

The extent of renal excretion of a compound is the net result of glomerular filtration, tubular secretion, and reabsorption.[1,2,4] The glomerular filtration is the ultrafiltration of about 10% of total renal blood flow at the glomerulus of the nephron, resulting in a mean glomerular filtration rate (GFR[a]) of 125 mL/min in a 70 kg young man.[4,5] Clearance by glomerular filtration equals the product of GFR and plasma free fraction (fu). Tubular secretion facilitates transport from the plasma into proximal tubular lumen. Because of involvement of active transporters, the secretion process is saturable and may be inhibited by coadministrated drugs, suggesting the possibility of clinical drug−drug interactions.[6−8] Most compounds undergo tubular reabsorption from urine into blood all along the nephron because of the high concentration gradient created by the water reuptake process.[1,2] The degree of reabsorption mainly depends on passive permeability and is influenced by the urine flow and pH. However, uptake and efflux transporters localized at proximal tubuli may contribute to the reabsorption process.[9,10] The net secretion or net reabsorption is apparent when renal clearance is greater than fu*GFR or renal clearance is less than fu*GFR, respectively, although both secretory and reabsorption processes may be occurring simultaneously. Unlike tubular reabsorption, apparent low passive permeability across basolateral membrane compared to apical membrane[1] and a high counter concentration gradient created by water reabsorption make contribution of passive tubular secretion negligible, if any. Therefore, transporters mainly contribute to the secretory transport, which thus depends on the transporter kinetics, plasma free fraction, and the blood flow rate.[6,7]

Organic anion transporters (OAT1 and OAT3) and organic cationic transporters (OCT2 and OCT3), localized in the basolateral membrane, play a key role in tubular secretion of drugs.[11,12] ATP-binding cassette (ABC) transporters, P-glycoprotein, and multidrug resistant proteins (MRP2 and MRP4) are localized on the brush border membrane and transport substrates from cells to lumen (urine), hindering reabsorption or facilitating secretion.[13,14] Other known transporters expressed in the human kidney include OATP4C1, OCTN1, OCTN2, PEPT2, OAT4, MATE, and URAT1.[15]

The biochemical composition of the membrane bilayer imposes certain characteristic features among molecules that have to translocate through these membranes. The dependence of passive permeability via transcellular and paracellular pathways on the compound physicochemical properties like cLogP, molecular size, hydrogen bonding capacity, and polar surface area (PSA) has been demonstrated in a number

*To whom correspondence should be addressed. Telephone: +1-860-715-0257. Fax: +1-860-441-6402. E-mail: manthena.v.varma@pfizer.com.

[a] Abbreviations: ABC, ATP-binding cassette; CL_r, renal clearance; CL_{total}, total body clearance; fu, plasma free fraction; GFR, glomerular filtration rate; HBA, hydrogen bond acceptors; HBD, hydrogen bond donors; OAT, organic anion transporter; OCT, organic cation transporter; PSA, polar surface area; Rb, free rotatable bond; RPSA, relative polar surface area.

 Published on Web 05/15/2009

Table 1. Mean (Median) Physicochemical Properties for the Human Renal Clearance Ranges

CL_r bins [(mL/min)/kg]	*n*	CL_r [(mL/min)/kg]	CL_{total} [(mL/min)/kg]	MW	cLogP	$cLogD_{7.4}$	PSA [Å^2]	RPSA [%]	free rotable bonds	H-donors	H-acceptors
< 0.1	102	0.03	5.29	377	2.8	1.7	89.3	24.3	5.7	1.7	6.1
		(0.01)	(2.45)	(336)	(2.7)	(1.8)	(74.4)	(22.9)	(5)	(1)	(5)
0.1−0.5	78	0.25	6.70	377	2.4	0.9	89.8	23.2	6.2	2.3	6.3
		(0.22)	(4.50)	(321)	(2.5)	(1.4)	(77.9)	(23.1)	(5)	(1)	(5)
0.5−1	48	0.75	6.24	361	1.6	−0.1	99.6	29.7	6.6	2.9	6.4
		(0.74)	(3.90)	(346)	(1.8)	(0.5)	(83.6)	(24.2)	(6)	(2)	(6)
1−3	104	1.86	8.54	377	0.8	−1.4	120.7	35.2	6.3	3.6	7.5
		(1.70)	(3.20)	(350)	(1.1)	(−1.3)	(108.0)	(33.3)	(6)	(3)	(7)
> 3	59	5.15	10.94	299	0.5	−1.0	96.4	33.7	5.3	2.6	6.3
		(4.42)	(8.30)	(277)	(0.7)	(−1.0)	(96.4)	(33.4)	(5)	(2)	(6)

of occasions, which resulted in various qualitative, semiquantitative and quantitative structure−permeability relationship models.[16−18] Lipinski's pioneer work proposed a simple set of rules that is well accepted in drug research industry.[18] Although most of these models were intended to predict the oral drug absorption, the fundamental parameter associated with the physicochemical properties is bilayer membrane permeability, which plays an important role in the distribution and elimination of drugs, as well.

As mentioned above, renal clearance is determined by the absorptive and secretory permeability across the tubular epithelia, which in turn is influenced by the complex bidirectional passive and active tubular transport mechanisms. Apart from a few studies on a limited series of structurally related compounds, the physicochemical determinants of human renal clearance is largely unexplored.[19] This study describes the relationships between physicochemical properties and the human renal clearance, using a large data set of 391 drugs or compounds tested in humans. We also evaluated the differences in the physicochemical property profiles of the renal net secreted versus net reabsorbed compounds with the objective to identify the properties influencing either process. Statistical analysis suggested that certain physicochemical property cutoffs can be used to identify those compounds that will undergo net secretion, for which contribution of renal clearance is expected to be high and a possible risk of renal drug−drug interactions exists.

Methods

A database of 391 compounds was developed after carefully and exhaustively mining the scientific literature for relevant human pharmacokinetic parameters. Human renal clearance (CL_r) data were mainly obtained from the literature when the individual reports calculated CL_r from the unchanged amount excreted in urine (Ae_{iv}) and plasma area under the curve (AUC_{iv}) following intravenous dosing, using eq 1.

$$CL_r = \frac{Ae_{iv}}{AUC_{iv}} \quad (1)$$

To extend the database, CL_r data following oral dosing were included when the reported parameter was calculated (eq 2) from the unchanged amount excreted in urine (Ae_{Oral}) and plasma area under the curve (AUC_{Oral}).

$$CL_r = \frac{Ae_{oral}}{AUC_{oral}} \quad (2)$$

The human total body clearance (CL_{total}) and the plasma free fraction (fu) were taken from the literature compilation reported by Obach et al.[20] The pharmacokinetic data were exclusively obtained from reports in which healthy young adult subjects were studied or patient populations whose health or physiological condition is not severely compromised with respect to total and renal clearance. For some classes of compounds, for example, anticancer and anti-HIV compounds, data were only available from patient populations and/or populations taking concomitant medications, and in these instances, the data were included. To our knowledge, this data base available as Supporting Information, is the largest of its kind in the literature.[21,22]

The compounds in the database were binned into (i) compounds with net renal reabsorption ($CL_r < 0.8 \cdot fu \cdot GFR$), (ii) compounds with net renal secretion ($CL_r > 1.2 \cdot fu \cdot GFR$), and (iii) compounds with no net reabsorption or secretion ($0.8 \cdot fu \cdot GFR < CL_r < 1.2 \cdot fu \cdot GFR$). Mean physiological GFR of 1.78 (mL/min)/kg[4,5] was used in the process of categorizing, and a 20% tolerance was incorporated in order to clearly distinguish secreted compounds and the reabsorbed compounds.

Physicochemical properties were computed for the 391 compounds, for which the CL_r and fu data were available, using an in-house program. These properties include molecular weight (MW), calculated *n*-octanol/water partition coefficient (cLogP, ACD), calculated *n*-octanol/water distribution coefficient ($cLogD_{6.3}$ and $cLogD_{7.4}$, ACD; subscript indicates pH), molecular surface area (MSA, Pipeline Pilot), polar surface area (PSA in Å^2, ACD), number of free rotatable bonds (Rb), and number of hydrogen bond donors (HBD) and acceptors (HBA). The relative polar surface area (% RPSA = (PSA/MSA) × 100) was also calculated.

Standard statistical tests have been carried out to analyze the differences in the renal clearance and physicochemical properties of various data subsets. The parametric *t*-test (unpaired, two-tailed, unequal variance) was employed to determine the significance at the 95% confidence level. However, data were also analyzed by the nonparametric Mann−Whitney test (two-tailed), as the distributions of some properties are skewed away from the normality.[23]

Results

Relationship between Physicochemical Properties and Renal Clearance. Table 1 shows the trend of physicochemical properties of the compounds that are binned based on their human renal clearance range. Mean cLogP and $cLogD_{7.4}$ are higher for compounds with low renal clearance. Although molecular weight showed no particular trend, it is interesting to note that a subset of compounds with high renal clearance ($CL_r > 3$ (mL/min)/kg) have significantly lower molecular weight ($p < 0.001$) compared to the rest of the data set. On average, polar descriptors (PSA, RPSA, and hydrogen bond count (HBD + HBA)) showed decreasing trend with a decrease in renal clearance, with the exception of compounds with renal clearance of > 3 (mL/min)/kg. Figure 1 shows the relationship between physicochemical properties and renal clearance. It is noted that trends could

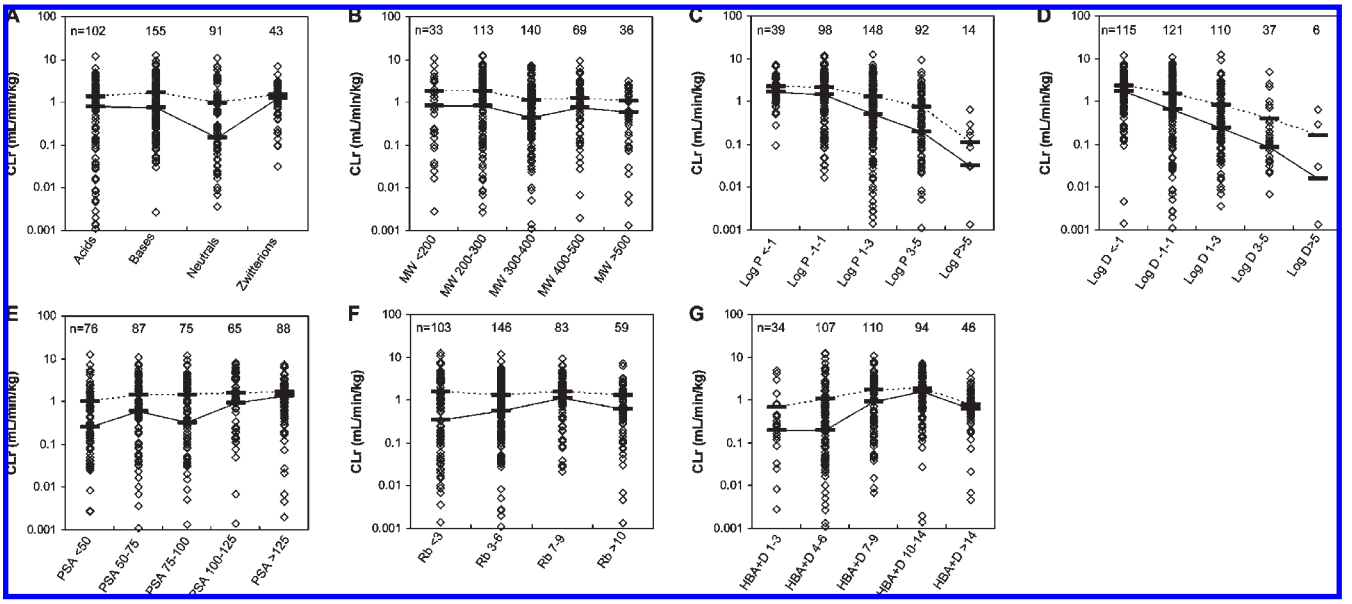

Figure 1. Relationship between human renal clearance and (A) ionization state, (B) molecular weight, (C) cLogP, (D) cLogD, pH 7.4, (E) PSA [Å^2], (F) number of Rb, and (G) number of hydrogen bond donors and acceptors. Dotted and solid lines denote mean and median values, respectively.

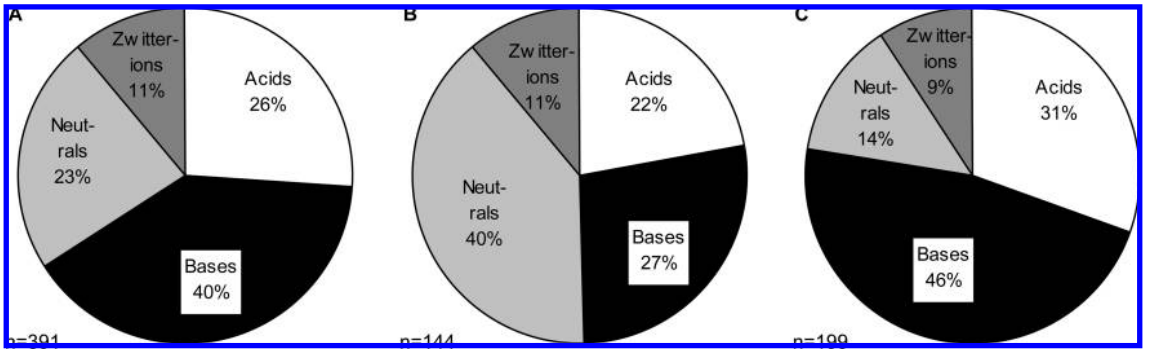

Figure 2. Ionization state distribution of (A) all compounds in the database and the subsets of compounds that showed (B) net reabsorption and (C) net secretion.

not be easily observed with mean values for some physicochemical properties because of the scattered and overlap in the data. However, median values give a clear picture of this large data set. The data set indicated that neutral compounds have low renal clearance compared to the other ionization states. Lipophilicity, cLogP and cLogD$_{7.4}$, showed a clear trend, with highly lipophilic compounds tending to show minimal renal clearance. cLogD at mean urinary pH (pH 6.3)[4] showed similar trend (data not shown), although compounds with pK_a in the critical region may have different values from the cLogD$_{7.4}$. Median renal clearance values also showed trends with PSA, number of Rb, and hydrogen bond count. Apparently, high renal clearance is associated with a high PSA, high number of Rb, and hydrogen bond count.

Physicochemical Property Profiles of Net Secreted Compounds and Net Reabsorbed Compounds. Compounds in the data set were categorized to subsets of net reabsorbed and net secreted compounds based on their plasma free fraction (fu) and the renal clearance as given in Methods. Figure 2 shows the ionization state distribution of the complete data set and the net reabsorbed and net secreted compounds subsets. It is apparent that more than 75% of the net secreted compounds are acids and bases, while only 50% of reabsorbed compounds are acids or bases. Also, 40% of the reabsorbed compounds are neutrals, while only 14% secreted compounds are found to be neutrals. Furthermore, median renal clearance of the reabsorbed neutrals and zwitterions (0.04 (mL/min)/kg) is significantly lower ($p < 0.01$) than that of the reabsorbed acids and bases (0.11 (mL/min)/kg), indicating that neutral and zwitterionic compounds are predominantly reabsorbed.

A summary of properties (Table 2) and the cumulative fraction curves (Figure 3) reveal that certain physicochemical properties of the two subsets, net reabsorbed and net secreted, differ from each other significantly. Secreted compounds have insignificant but slightly higher molecular weight compared to reabsorbed compounds. Although no difference in the cLogP distribution between two subsets was found, cLogD$_{7.4}$ profiles significantly differ ($p < 0.001$). cLogD at mean urinary pH (pH 6.3)[4] showed similar difference (data not shown). Clearly, secreted compounds tend to be hydrophilic. About 50% of the net secreted compounds have cLogD$_{7.4} < 0$, while 50% of net reabsorbed compounds have cLogD$_{7.4} > 1.2$ (Figure 3C). Profile differences were also obvious for PSA, number of Rb, and hydrogen bond count. In general, secreted compounds tend to show higher PSA, number of Rb, and hydrogen bond count; however, it is

Table 2. Summery of Physicochemical Properties for the Human Renal Clearance Data Set, Categorized to Tubular Reabsorption and Active Secretion, Based on fu·GFR Vs Renal Clearance

data sets[a]	n	CL_r [(mL/min)/kg]	CL_{total} [(mL/min)/kg]	MW	cLogP	$cLogD_{7.4}$	PSA [Å^2]	RPSA [%]	free rotable bonds	H-donors	H-acceptors
all	391										
mean		1.42	7.40	363	1.70	0.10	100.1	29.0	6.0	2.6	6.6
median		0.64	4.00	334	1.75	0.35	84.5	26.8	5.0	2	6
range		0.0−12.5	0−85	76−1880	(−5.1)−8.9	(−10.1)−7.4	3−764	1−90	0−42	0−29	1−46
(G) CL_r = GFR·fu	48										
mean		0.87	6.43	361	1.24	−0.44	110.4	32.0	6.0	3.4	7.0
median		0.92	3.20	308	1.33	−0.22	81.9	30.0	5.0	2	5
range		0.0−2.0	0−28	126−1880	(−4.1)5.6	(−7.5)−4.3	3−662	1−39	0−34	0−25	1−42
(R) reabsorbed	144										
mean		0.23	5.51	362	1.88	0.73	93.1	27.3	5.4	2.2	6.3
median		0.07	2.40	326	2.15	1.15	78.9	25.7	4.5	1	5
range		0.0−1.4	0−37	76−1706	(−(5.1)−7.8	(−10.1)−6.1	12−764	4−90	0−42	0−29	1−46
(S) secreted	199										
mean		2.41[b,c]	9.00[b,c]	364	1.69	−0.22[b,c]	102.6[c]	29.6	6.4[b,c]	2.7[c]	6.6[c]
median		1.90	5.20	345	1.61	−0.22	92.5	27.1	6.0	2	6
range		0.0−12.5	0−85	129−854	(−4.3)−8.9	(−7.5)−7.4	3−288	1−76	0−17	0−12	1−15

[a] (G) 0.8·fu·GFR < Cl_r < 1.2·fu·GFR. (R) net tubular reabsorption, CL_r < 0.8·fu·GFR. (S) net tubular secretion, CL_r > 1.2·fu·GFR. [b] p < 0.05, unpaired (two-tailed) t-test assuming unequal variance, compared to reabsorbed compounds. [c] p < 0.05, Mann−Whitney (two-tailed, nonparametric) t-test, compared to reabsorbed compounds.

interesting to note that the ranges of these properties are tighter for secreted compounds (Table 2).

The scattered relationship plot between $cLogD_{7.4}$ and renal clearance also revealed that compounds showing net secretion are generally ionized at physiological pH and are hydrophilic (Figure 4). In the case of acids, more than 85% of compounds with $cLogD_{7.4} < -1$ yielded net renal secretion, while 82% of bases with cLogD < 0 showed net secretion. However, only 50% of neutral and zwitterions with $cLogD_{7.4} < 0$ fall into this category. Furthermore, hydrophilic secreted compounds showed a significantly higher renal clearance (Figure 4 insets). For example, median renal clearance of the secreted acids with $cLogD_{7.4} < -1$ was 5.7-fold higher than the lipophilic secreted acids ($p = 0.002$). Similar difference was also evident for secreted bases and neutral and zwitterionic compounds. These results, along with the ionic distribution of the secreted compounds (Figure 2), clearly suggest that hydrophilic acids and bases are more probable compounds secreted in clinic.

Therapeutic Area versus Renal Clearance. Finally, the therapeutic indications of the compounds in the data set were grouped into six major therapeutic areas,[24,25] as we attempted to evaluate the significance of renal clearance in each therapeutic area. Figure 5A shows the percentage of compounds with renal clearance more than 50% of the total body clearance, in different therapeutic areas. Of all the compounds (391) in the data set, 123 (31%) compounds showed predominant renal contribution to the total body clearance. Apparently, renal clearance is the primary elimination route for about 60% of the anti-infection compounds, while 89% of 110 nervous system compounds take alternative elimination routes. Renal clearance also seems to play a primary role in the disposition of a number of cardiovascular and gastrointestinal/metabolism drugs. In the cardiovascular, cancer, and infection therapeutic areas, more compounds tend to show net secretion in clinic, while nervous system compounds are predominantly reabsorbed (Figure 5B).

The differences in renal clearance and physicochemical properties between infection and nervous system therapeutic areas were found to be statistically significant (Table 3). Median renal clearance of the compounds in therapeutic areas are in the rank-order of infection > cardiovascular > cancer > nervous system > GI/metabolism > respiratory inflammation. Compounds in the high renally cleared infection therapeutic area subset showed significantly lower lipophilicity (cLogP and $cLogD_{7.4}$) compared to other classes of compounds while showing high molecular weight, PSA, hydrogen bond count, and number of Rb. Nervous system compounds tend to have higher lipophilicity and lower molecular weight, PSA, number of Rb, and hydrogen bond count and are found to have low renal clearance. The other sizable subset, cardiovascular compounds, showed median renal clearance and physicochemical properties typically between that of infection and nervous system compounds.

Discussion

Renal clearance is the net result of three processes: glomerular filtration, active tubular secretion, and reabsorption.[1,2] We hypothesize that the compounds with sufficient passive permeability can be efficiently reabsorbed, as the passive reabsorption process occurs throughout the length of the nephron, against the secretion predominantly occurring at the proximal tubule. Therefore, the physicochemical determinants of passive membrane permeability may reasonably describe the renal drug clearance. In this study, we analyzed the interrelation of the most widely accepted physicochemical properties and the human renal clearance of 391 drugs tested in the clinic.

One of the distinctive trends that can be drawn from this analysis is that the renal clearance decreases with increase in lipophilicity, cLogP and cLogD (Figure 1C and 1D). The negative correlation with increasing lipophilicity can be interpreted as a result of an increase in passive reabsorption, resulting in less renal clearance and a probable masking of tubular secretion, partially or completely, if any. Lipophilicity was also shown to influence the protein binding, which in turn determines the fu·GFR factor of renal clearance. Obach et al., using a set of 554 compounds, suggested that increasing lipophilicity typically yields increased plasma protein binding

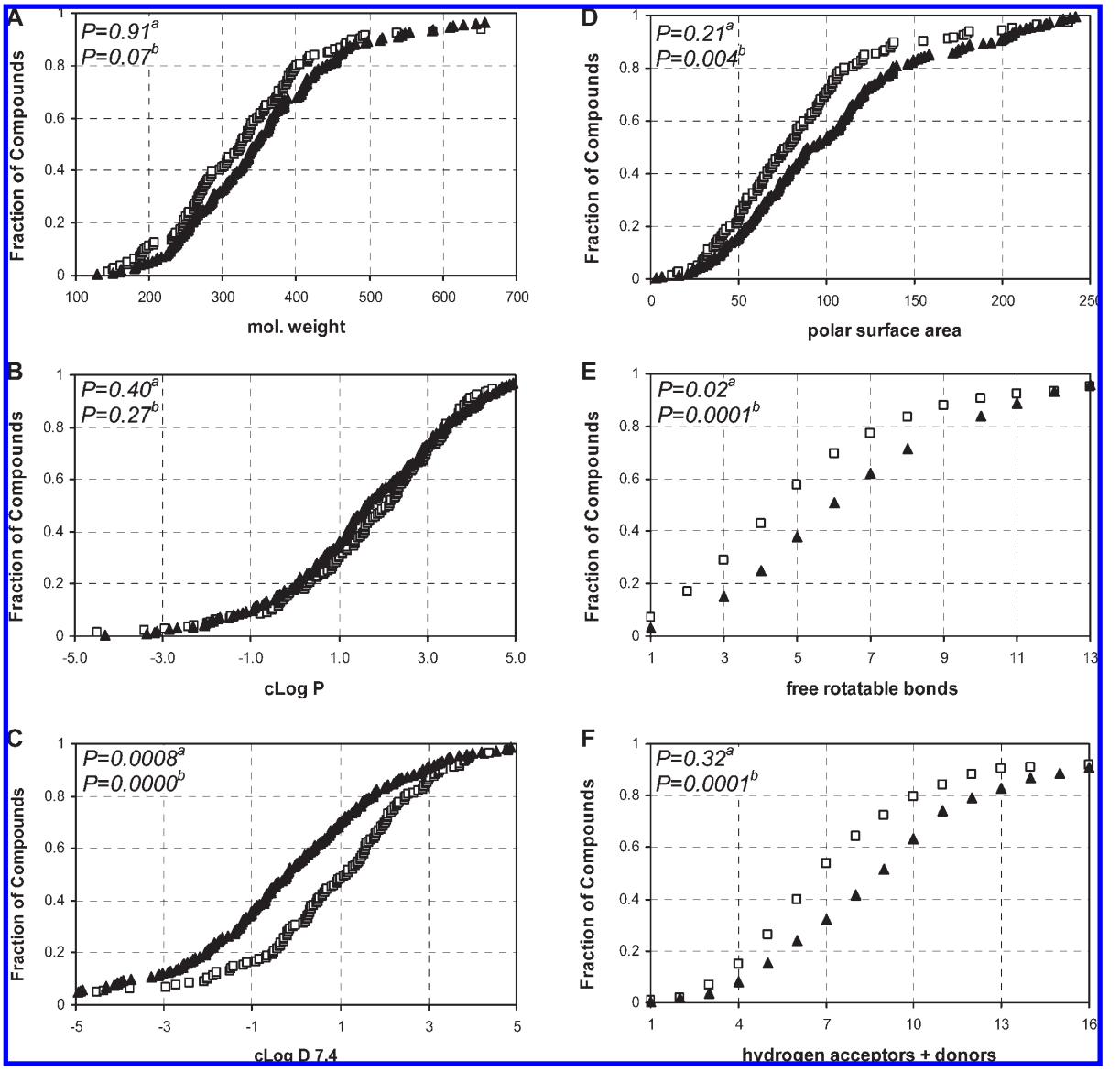

Figure 3. Frequency distribution and differences in molecular weight, cLogP, cLogD pH 7.4, PSA [Å^2], number of Rb, and number of hydrogen donors and acceptors of compounds that showed net reabsorption (open square) and net secretion (closed triangle). The *X*-axes of the plots were limited (13 for Rb and 16 for HBA and HBD) for clarity. Superscript "a" denotes unpaired (two-tailed) *t*-test assuming unequal variance. Superscript "b" denotes Mann−Whitney (two-tailed, nonparametric) *t*-test.

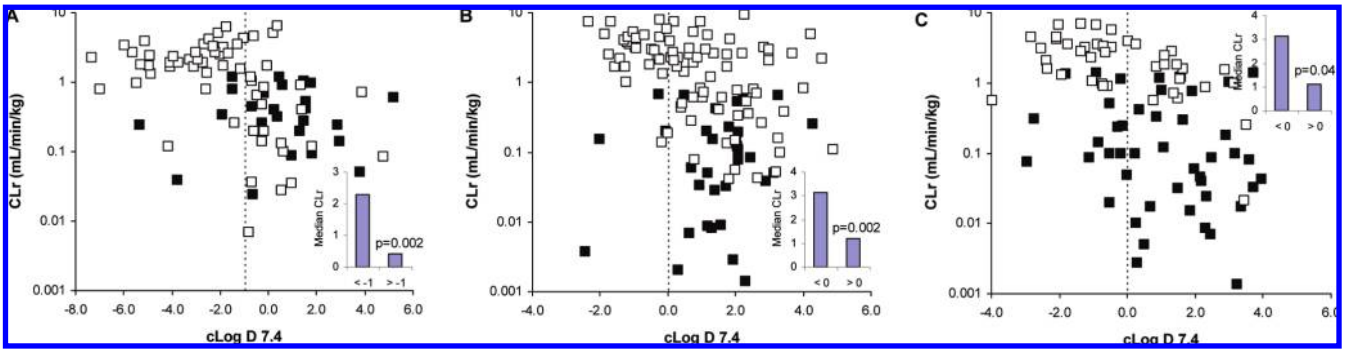

Figure 4. Relationship between cLogD$_{7.4}$ and renal clearance of (A) acidic, (B) basic, and (C) neutral + zwitterionic compounds. Closed points indicate reabsorbed compounds, and open points indicate secreted compounds. Inset shows median renal clearance of secreted compounds in two cLogD$_{7.4}$ bins. Statistical significance was tested using unpaired *t*-test (two-tailed).

because of the hydrophobic forces driven interaction with albumin and α1-acid glycoprotein.[20] Membrane permeability requires lipid solubility as well as desolvation of associated hydrogen-bonded water molecules.[26,27] The positive correlation with polar descriptors (PSA, RPSA, and hydrogen bond count) can therefore be attributed to their effect of passive

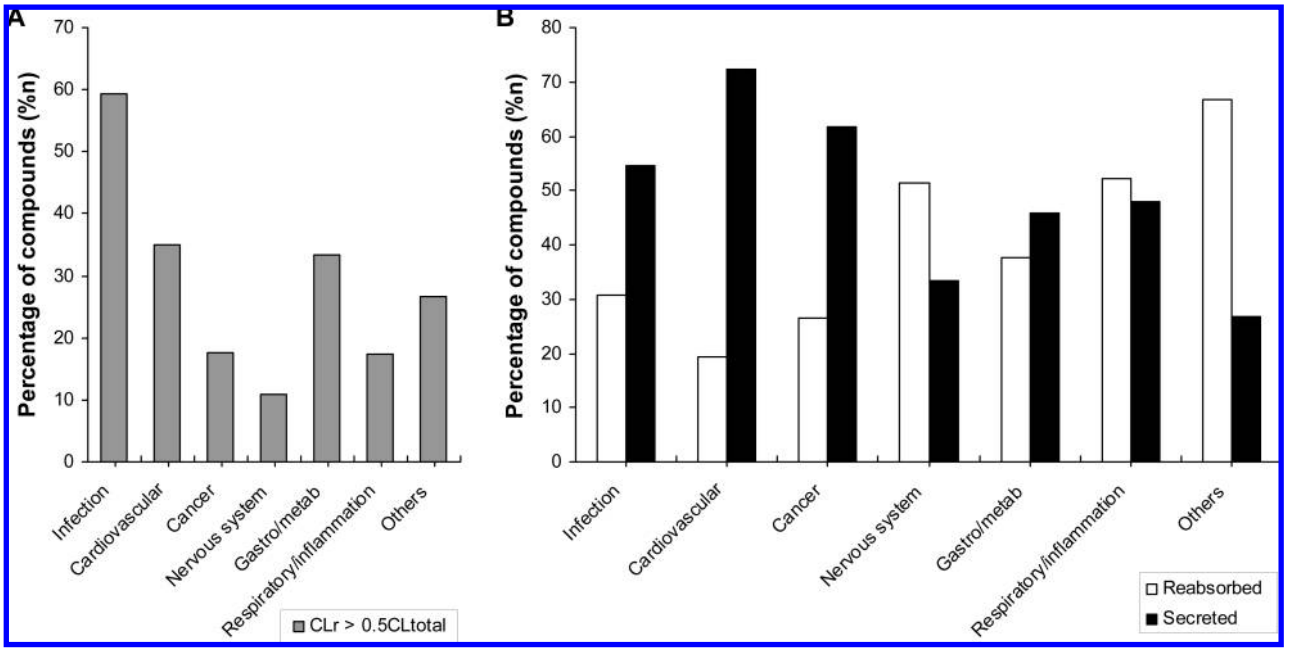

Figure 5. (A) Percentage of compounds that show significant renal clearance contribution to the clinical total body clearance (CL_{total}). (B) Percentage of compounds with net tubular reabsorption (open bars) and net secretion (closed bars) in each therapeutic area.

Table 3. Mean, Median, Range, and Statistics of Clearance and Physicochemical Properties of Subsets of Compounds by Therapeutic Areas[a]

therapeutic area	n	CLr [mL/min/kg]	CLtotal [mL/min/kg]	mol weight	clogP	clogD pH7.4	PSA [Å^2]	RPSA [%]	free rot. bonds	H-donors	H-acceptors	Ionic Distribution[g]
infection	101											
mean		1.82	3.83	423	0.24	-2.17	154.6	40.1	6.8	4.2	9.5	
median		1.41	2.50	375	0.61	-2.00	135.0	41.2	5	3	8	
range		0.0-7.3	0-25	126-1880	(-5.1)-6.2	(-10)-4.3	26-764	8-95	1-42	0-29	1-46	
statistics		d,f	b,c,d	b,d,e	b,c,d,e,f	b,c,d,e,f	b,d,e,f	b,d,e,f	d	b,d,e,f	b,d,e,f	
cardiovascular	84											
mean		1.77	8.95	342	2.45	0.81	83.9	25.3	7.3	2.4	5.7	
median		0.90	5.50	345	2.54	0.65	82.6	25.5	7	2	5	
range		0.0-12.0	0-85	160-781	(-1.0)-8.9	(-3.1)-6.9	12-203	4-56	0-14	0-6	1-14	
statistics		d,f	a,e	a,d	a,c	a	a,c,d,e	a,c,d,e	d,f	a,c,d	a,c,d	
cancer	34											
mean		1.27	11.93	426	1.37	0.33	132.5	37.2	6.8	3.6	8.6	
median		0.74	6.45	369	1.02	0.23	108.2	35.6	6	3	8	
range		0.0-5.2	0-130	76-1300	(-3.2)-7.4	(-7.0)-7.4	41-534	14-90	0-17	0-12	3-29	
statistics		-	a	d	a,b,d,f	a	b,d	b,d	d	b,d,f	b,d,f	
nervous system	110											
mean		1.02	9.64	303	2.40	1.32	52.3	18.2	4.2	1.1	4.2	
median		0.24	7.60	300	2.47	1.51	50.2	16.3	4	1	4	
range		0.0-12.5	0-41	144-653	(-4.3)-6.1	(-4.3)-6.1	3-130	1-52	0-10	0-5	1-9	
statistics		a,b	a,e	a,b,c,e	a,c	a,e	a,b,c,e,f	a,b,c,e,f	a,b,c,e	a,b,c,e,f	a,b,c,e,f	
gastro/metab	24											
mean		1.81	4.70	348	1.76	0.23	105.8	33.2	6.5	2.5	6.4	
median		0.11	3.85	347	2.28	0.97	96.6	28.5	6	2	6	
range		0.0-7.9	0-18	129-494	(-2.9)-4.7	(-8.3)-2.8	36-233	9-72	0-14	0-5	4-9	
statistics		-	d,b	a,d	a	a,d	a,b,d	a,b,d	d	a,d	a,d	
respiratory/inflam	23											
mean		0.68	5.51	380	2.57	0.92	95.0	26.8	5.2	2.2	5.8	
median		0.09	2.50	343	2.55	0.80	82.6	24.9	4	2	5	
range		0.0-5.0	0-56	194-1200	0.0-7.8	(-1.9)-5.2	37-279	17-46	2-16	1-5	2-23	
statistics		a,b	-	-	a,c	a	a,d	a,d	b	a,c,d	a,c,d	

[a] Therapeutic areas arranged in the order of decreasing median renal clearance. Statistics: $p < 0.05$ (t-test) compared to (a) infection, (b) cardiovascular, (c) cancer, (d) nervous system, (e) gastrointestinal and metabolism, and (f) respiratory and inflammation. [g] Ionic distribution color coding as in Figure 2.

reabsorption process. For this data set, the calculated PSA correlated closely ($r = 0.94$) with the hydrogen bond count, suggesting that these physicochemical properties are closely associated and influence the involved processes to a similar extent. Increasing renal clearance is also paralleled by increasing the number of Rb, apparently due to decreasing permeation rate. Veber et al. observed a negative correlation between artificial membrane permeation rates and the average rotatable

count using a data set of 3061 compounds and proposed that the correlation may reflect a possible entropic cost of changes in conformation required for the molecule to present an appropriate exterior to the hydrocarbon interior of the membrane.[28]

Ionization state plays a key role in defining the membrane permeability.[29] Molecules ionized at the physiological pH tend to interact with the charged membrane contents, resulting in a low permeability. And therefore, neutral molecules are generally found to be the highly permeable, followed by bases, acids, and zwitterions. We observed that neutral compounds on average are less cleared renally, presumably as a result of significant reabsorption due to high membrane permeability.

One of the major goals of this study is to distinguish between net reabsorbed and net secreted groups of compounds based on the physicochemical property profiles. No significant difference in the profiles of molecular weight and cLogP was evident between the two subsets (Figure 3). However, cLogD, polar descriptors (PSA, HBA + HBD), and number of rotatable bonds showed significant differences, suggesting that these properties are of more fundamental importance in renal drug clearance. Of particular interest is the ionization state distribution and cLogD profiles (Figures 2 and 4). The evident difference in ionization state distribution between the net reabsorbed and net secreted subsets clearly implies that acids and bases are more likely to be secreted. Furthermore, most hydrophilic acids ($cLogD_{7.4} < -1$) and hydrophilic bases ($cLogD_{7.4} < -0$) yielded net secretion, suggesting that these descriptors are important determinants for the affinity to the secretory transport systems localized at the proximal tubuli.[30,31] Nevertheless, lipophilic acids and bases may also be substrates to the transport systems; however, increased passive reabsorption for such compounds may result in no observable net secretion.

It is recognized that the polyspecific members of the organic ion transporter family (SLC 22) primarily localized at the proximal tubuli play an important role in the renal secretion process, and the members consist of OCTs and OATs.[32−34] Hydrophobicity and basicity are indicated to be the principal determinants of substrate interaction with OCTs, while hydrophobicity and acidity are associated with OATs interaction.[31] However, most of the high affinity substrates to these transporters are relatively hydrophilic ($cLogP < 0$).[30,32] Furthermore, hydrogen bonding ability seems to be an advantageous mechanism to stabilize the substrate−transporter complex.[31] Collectively, hydrophilic and ionized compounds with hydrogen bonding ability are most likely to be secreted in the clinic (i) mainly because of their ability to interact with the renal transporter systems at the proximal tubuli and (ii) because they do not possess appropriate physicochemical descriptors to undergo reabsorption process along the length of the nephron.

Literature reports indicated that human renal transporters have a strong influence on the pharmacokinetics and toxicokinetics of many druglike chemicals and that competition for binding and transport may result in drug−drug interactions.[6,7,35,36] We believe that the discriminating physicochemical profiles can be used to predict the potential for a renal drug−drug interaction. For example, two hydrophilic bases ($cLogD < 0$) with predominate renal elimination are more likely to result in clinical interaction. This can be further exemplified with the literature reports. Probenecid, a hydrophilic acid and known to interact with OAT, shows more than 40% inhibition in renal clearance of primarily renally cleared hydrophilic acids like azlocillin, pencillin G, famotidine, and chlorthiazide.[6,35,37] Similarly, studies have shown that hydrophilic bases and OCT substrates like cimetidine and ranitidine significantly reduce renal clearance of hydrophilic bases like bisoprolol, metformin, nicotine, and procainamide.[38−40]

The physicochemical property profiles across therapeutic areas are similar to those reported earlier.[25,41] Most nervous system compounds are centrally acting, and their physicochemical properties are consistent with the requirement of lipophilicity and low PSA for efficient brain penetration.[42,43] However, these compounds tend to have limited renal clearance due to this property profile. In contrast, property distribution among infection compounds shows different trends from the other therapeutic areas. The significantly lower lipophilicity and higher hydrogen bonding descriptors are consistent with the apparent high renal clearance for this subset. Overall, categorizing into subsets of therapeutic areas further substantiates the relationships between the physicochemical properties and the renal clearance, observed with the whole data set.

We further explored the chemical space in the infection therapeutic area subset, which had 55 secreted compounds. Notably, all penicillins (93%), except ampicillin, and 11 of 14 cephalosporin antibiotics in the database showed net secretion in the clinic. Takeda et al. reported that all eight tested cephalosporins interacted with hOAT1, hOAT2, and hOAT3.[44,45] However, in general, hOAT2 appears to interact the weakest with those cephalosporin antibiotics, suggesting that hOAT1 and hOAT3 play a distinct role in the transport of various cephalosporin antibiotics in the basolateral membrane of the proximal tubule. Jariyawat et al. demonstrated the inhibition of *p*-aminohippurate transport via rat-Oat1 by all of the penicillins and cephalosporins tested.[46] The findings from our study complement the finding that β-lactam antibiotics, hydrophilic compounds with a core chemical structure (β-lactam ring) and an anionic moiety, interact with renal OATs and predominately secrete into urine. In contrast to β-lactam antibiotics, only 50% of fluoroquinolones and no sulfa drugs showed net secretion. No distinct structural or physicochemical differences were observed between reabsorbed and secreted fluoroquinolones. Ullrich et al. demonstrated that fluoroquinolones not possessing a piperazine group interact moderately with the OATs, whereas compounds with an additional piperazine group interact weakly.[47] However, no such discrimination was observed to help distinguish between reabsorbed and secreted compounds with the current data set, as the compounds with presence and absence of a piperazine group are present in equal numbers in both subsets. Nevertheless, interaction with the renal secretory transporters does not necessarily indicate net secretion in clinic.

In the case of cardiovascular compounds structural features, of the 14 β-adrenoceptor antagonists containing an aryloxypropan-2-olamino unit as pharmacophore, only metoprolol showed net reabsorption. Although many cardiovascular drugs showed net secretion, further structural analysis was not possible because of the diverse chemical space. However, an examination of the literature reports reveled that many net secreted cardiovascular drugs in the current database interact with OCTs, presumably because of their basicity.[32,48]

In summary, we have compiled arguably the largest publicly available human renal clearance data set of diverse

chemical space and therapeutic areas. The data in this report show that renal clearance contributes to more than 50% of total body clearance for about 31% of the compounds, indicating the importance of predicting renal clearance in the process of reliable pharmacokinetic predictions. This is particularly important for compounds predicted to have low or negligible metabolic and biliary clearances, especially in the therapeutic areas like infection and cardiovascular. Analysis of the most easily accessible and widely used physicochemical properties suggests that relationships using these descriptors are capable of providing meaningful interpretations concerning renal drug disposition. Ionization state, lipophilicity, and polar descriptors are found to be the physicochemical determinants of human renal clearance. We also note that hydrophilic and ionized compounds show net secretion due to the favorable interaction with the renal transporters and ability of such compounds to avoid reabsorption of proximally secreted amounts in the distal and collecting tubules. Nevertheless, these physicochemical properties can be easily altered in a molecule to manipulate the drug disposition and achieve pharmacokinetic advantage with respect to drug exposure and clinical drug−drug interactions.

Supporting Information Available: An Excel worksheet of 391 compound names, CAS numbers, data on human renal clearance, total body clearance, fu·GFR, net reabsorbed versus net secretion category, therapeutic area, and appropriate literature references. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Masereeuw, R.; Russel, F. G. Mechanisms and clinical implications of renal drug excretion. *Drug Metab. Rev.* **2001**, *33*, 299–351.
(2) Fagerholm, U. Prediction of human pharmacokinetics: renal metabolic and excretion clearance. *J. Pharm. Pharmacol.* **2007**, *59*, 1463–1471.
(3) Roffey, S. J.; Obach, R. S.; Gedge, J. I.; Smith, D. A. What is the objective of the mass balance study? A retrospective analysis of data in animal and human excretion studies employing radiolabeled drugs. *Drug Metab. Rev.* **2007**, *39*, 17–43.
(4) Roland, M.; Tozer, T. N. Clinical Pharmacokientics: Concepts and Applications; Williams & Wilkins: Baltimore, MD, 1995.
(5) Walton, K.; Dorne, J. L.; Renwick, A. G. Species-specific uncertainty factors for compounds eliminated principally by renal excretion in humans. *Food Chem. Toxicol.* **2004**, *42*, 261–274.
(6) Ho, R. H.; Kim, R. B. Transporters and drug therapy: implications for drug disposition and disease. *Clin. Pharmacol. Ther.* **2005**, *78*, 260–277.
(7) Shitara, Y.; Sato, H.; Sugiyama, Y. Evaluation of drug−drug interaction in the hepatobiliary and renal transport of drugs. *Annu. Rev. Pharmacol. Toxicol.* **2005**, *45*, 689–723.
(8) Li, M.; Anderson, G. D.; Wang, J. Drug−drug interactions involving membrane transporters in the human kidney. *Expert Opin. Drug Metab. Toxicol.* **2006**, *2*, 505–532.
(9) Sun, H.; Frassetto, L.; Benet, L. Z. Effects of renal failure on drug transport and metabolism. *Pharmacol. Ther.* **2006**, *109*, 1–11.
(10) Jappar, D.; Hu, Y.; Keep, R. F.; Smith, D. E. Transport mechanisms of carnosine in SKPT cells: contribution of apical and basolateral membrane transporters. *Pharm. Res.* **2009**, *26*, 172–181.
(11) Koepsell, H.; Lips, K.; Volk, C. Polyspecific organic cation transporters: structure, function, physiological roles, and biopharmaceutical implications. *Pharm. Res.* **2007**, *24*, 1227–1251.
(12) El-Sheikh, A. A.; Masereeuw, R.; Russel, F. G. Mechanisms of renal anionic drug transport. *Eur. J. Pharmacol.* **2008**, *585*, 245–255.
(13) van de Water, F. M.; Masereeuw, R.; Russel, F. G. Function and regulation of multidrug resistance proteins (MRPs) in the renal elimination of organic anions. *Drug Metab. Rev.* **2005**, *37*, 443–471.
(14) Ci, L.; Kusuhara, H.; Adachi, M.; Schuetz, J. D.; Takeuchi, K.; Sugiyama, Y. Involvement of MRP4 (ABCC4) in the luminal efflux of ceftizoxime and cefazolin in the kidney. *Mol. Pharmacol.* **2007**, *71*, 1591–1597.
(15) Shitara, Y.; Horie, T.; Sugiyama, Y. Transporters as a determinant of drug clearance and tissue distribution. *Eur. J. Pharm. Sci.* **2006**, *27*, 425–446.
(16) Winiwarter, S.; Bonham, N. M.; Ax, F.; Hallberg, A.; Lennernas, H.; Karlen, A. Correlation of human jejunal permeability (in vivo) of drugs with experimentally and theoretically derived parameters. A multivariate data analysis approach. *J. Med. Chem.* **1998**, *41*, 4939–4949.
(17) Kelder, J.; Grootenhuis, P. D.; Bayada, D. M.; Delbressine, L. P.; Ploemen, J. P. Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs. *Pharm. Res.* **1999**, *16*, 1514–1519.
(18) Lipinski, C. A. Drug-like properties and the causes of poor solubility and poor permeability. *J. Pharmacol. Toxicol. Methods* **2000**, *44*, 235–249.
(19) Kubinyi, H. Lipophilicity and biological acitivity. Drug transport and drug distribution in model systems and in biological systems. *Arzneimittelforschung* **1979**, *29*, 1067–1080.
(20) Obach, R. S.; Lombardo, F.; Waters, N. J. Trend analysis of a database of intravenous pharmacokinetic parameters in humans for 670 drug compounds. *Drug Metab. Dispos.* **2008**, *36*, 1385–1405.
(21) Thummel, K. E.; Shen, D. D. Design and Optimization of Dosage Regimens: Pharmacokinetic Data. In Goodman and Gillman's the Pharmacological Basis of Therapeutics,10th ed.; Hardman, J. G., Limbird, L. E., Goodman Gilman, A., Eds.; McGraw-Hill: New York, 2001; pp 1917−2024.
(22) Doddareddy, M. R.; Cho, Y. S.; Koh, H. Y.; Kim, D. H.; Pae, A. N. In silico renal clearance model using classical Volsurf approach. *J. Chem. Inf. Model.* **2006**, *46*, 1312–1320.
(23) Wenlock, M. C.; Austin, R. P.; Barton, P.; Davis, A. M.; Leeson, P. D. A comparison of physiochemical property profiles of development and marketed oral drugs. *J. Med. Chem.* **2003**, *46*, 1250–1256.
(24) Doherty, A. In Annual Reports in Medicinal Chemistry; Academic Press: San Diego, CA, 2003; Vol. 38, pp 425−441.
(25) Leeson, P. D.; Davis, A. M. Time-related differences in the physical property profiles of oral drugs. *J. Med. Chem.* **2004**, *47*, 6338–6348.
(26) Goodwin, J. T.; Conradi, R. A.; Ho, N. F.; Burton, P. S. Physicochemical determinants of passive membrane permeability: role of solute hydrogen-bonding potential and volume. *J. Med. Chem.* **2001**, *44*, 3721–3729.
(27) Varma, M. V.; Sateesh, K.; Panchagnula, R. Functional role of P-glycoprotein in limiting intestinal absorption of drugs: contribution of passive permeability to P-glycoprotein mediated efflux transport. *Mol. Pharmaceutics* **2005**, *2*, 12–21.
(28) Veber, D. F.; Johnson, S. R.; Cheng, H. Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* **2002**, *45*, 2615–2623.
(29) Gleeson, M. P. Generation of a set of simple, interpretable ADMET rules of thumb. *J. Med. Chem.* **2008**, *51*, 817–834.
(30) Bednarczyk, D.; Ekins, S.; Wikel, J. H.; Wright, S. H. Influence of molecular structure on substrate binding to the human organic cation transporter, hOCT1. *Mol. Pharmacol.* **2003**, *63*, 489–498.
(31) Ullrich, K. J. Renal transporters for organic anions and organic cations. Structural requirements for substrates. *J. Membr. Biol.* **1997**, *158*, 95–107.
(32) Ahlin, G.; Karlsson, J.; Pedersen, J. M.; Gustavsson, L.; Larsson, R.; Matsson, P.; Norinder, U.; Bergstrom, C. A.; Artursson, P. Structural requirements for drug inhibition of the liver specific human organic cation transport protein 1. *J. Med. Chem.* **2008**, *51*, 5932–5942.
(33) Inui, K. I.; Masuda, S.; Saito, H. Cellular and molecular aspects of drug transport in the kidney. *Kidney Int.* **2000**, *58*, 944–958.
(34) Launay-Vacher, V.; Izzedine, H.; Karie, S.; Hulot, J. S.; Baumelou, A.; Deray, G. Renal tubular drug transporters. *Nephron Physiol.* **2006**, *103*, 97–106.
(35) Ayrton, A.; Morgan, P. Role of transport proteins in drug absorption, distribution and excretion. *Xenobiotica* **2001**, *31*, 469–497.
(36) Takeda, M.; Khamdang, S.; Narikawa, S.; Kimura, H.; Hosoyamada, M.; Cha, S. H.; Sekine, T.; Endou, H. Characterization of methotrexate transport and its drug interactions with human organic anion transporters. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 666–671.
(37) Inotsume, N.; Nishimura, M.; Nakano, M.; Fujiyama, S.; Sato, T. The inhibitory effect of probenecid on renal excretion of famotidine in young, healthy volunteers. *J. Clin. Pharmacol.* **1990**, *30*, 50–56.
(38) Bendayan, R.; Sullivan, J. T.; Shaw, C.; Frecker, R. C.; Sellers, E. M. Effect of cimetidine and ranitidine on the hepatic and renal elimination of nicotine in humans. *Eur. J. Clin. Pharmacol.* **1990**, *38*, 165–169.
(39) Kirch, W.; Rose, I.; Demers, H. G.; Leopold, G.; Pabst, J.; Ohnhaus, E. E. Pharmacokinetics of bisoprolol during repeated

oral administration to healthy volunteers and patients with kidney or liver disease. *Clin. Pharmacokinet*. **1987**, *13*, 110–117.
(40) Somogyi, A.; Stockley, C.; Keal, J.; Rolan, P.; Bochner, F. Reduction of metformin renal tubular secretion by cimetidine in man. *Br. J. Clin. Pharmacol*. **1987**, *23*, 545–551.
(41) O'Shea, R.; Moser, H. E. Physicochemical properties of antibacterial compounds: implications for drug discovery. *J. Med. Chem*. **2008**, *51*, 2871–2878.
(42) Mahar Doan, K. M.; Humphreys, J. E.; Webster, L. O.; Wring, S. A.; Shampine, L. J.; Serabjit-Singh, C. J.; Adkison, K. K.; Polli, J. W. Passive permeability and P-glycoprotein-mediated efflux differentiate central nervous system (CNS) and non-CNS marketed drugs. *J. Pharmacol. Exp. Ther*. **2002**, *303*, 1029–1037.
(43) van de Waterbeemd, H.; Camenisch, G.; Folkers, G.; Chretien, J. R.; Raevsky, O. A. Estimation of blood−brain barrier crossing of drugs using molecular size and shape, and H-bonding descriptors. *J. Drug Targeting* **1998**, *6*, 151–165.
(44) Takeda, M.; Babu, E.; Narikawa, S.; Endou, H. Interaction of human organic anion transporters with various cephalosporin antibiotics. *Eur. J. Pharmacol*. **2002**, *438*, 137–142.
(45) Khamdang, S.; Takeda, M.; Babu, E.; Noshiro, R.; Onozato, M. L.; Tojo, A.; Enomoto, A.; Huang, X. L.; Narikawa, S.; Anzai, N.; Piyachaturawat, P.; Endou, H. Interaction of human and rat organic anion transporter 2 with various cephalosporin antibiotics. *Eur. J. Pharmacol*. **2003**, *465*, 1–7.
(46) Jariyawat, S.; Sekine, T.; Takeda, M.; Apiwattanakul, N.; Kanai, Y.; Sophasan, S.; Endou, H. The interaction and transport of beta-lactam antibiotics with the cloned rat renal organic anion transporter 1. *J. Pharmacol. Exp. Ther*. **1999**, *290*, 672–677.
(47) Ullrich, K. J.; Rumrich, G.; David, C.; Fritzsch, G. Bisubstrates: substances that interact with both, renal contraluminal organic anion and organic cation transport systems. II. Zwitterionic substrates: dipeptides, cephalosporins, quinolone-carboxylate gyrase inhibitors and phosphamide thiazine carboxylates; nonionizable substrates: steroid hormones and cyclophosphamides. *Pfluegers Arch*. **1993**, *425*, 300–312.
(48) TP Search-Transporter database. TP-Search Production Committee. http://125.206.112.67/tp-search/index.html (accessed Feb 2009).