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Few Drugs Display Flip-Flop Pharmacokinetics and These Are Primarily Associated with Classes 3 and 4 of the BDDCS

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Abstract

Purpose—To determine the number of drugs exhibiting flip-flop pharmacokinetics following oral dosing from immediate release dosage forms and if they exhibit a common characteristic that may be predicted based on BDDCS classification.

Method—The literature was searched for drugs displaying flip-flop kinetics (i.e. absorption half-life larger than elimination half-life) in mammals in PubMed, via internet search engines and reviewing drug pharmacokinetic data.

Results—Twenty two drugs were identified as displaying flip-flop kinetics in humans (13 drugs), rat (9 drugs), monkey (3 drugs), horse (2 drugs), and/or rabbit (2 drugs). Nineteen of the 22 drugs exhibiting flip-flop kinetics were BDDCS Classes 3 and 4. One of the three exceptions, meclofenamic acid (Class 2), was identified in the horse however it would not exhibit flip-flop kinetics in humans where the oral dosing terminal half-life is 1.4 hr. The second, carvedilol, can be explained based on solubility issues, but the third sapropterin dihydrochloride (nominally Class 1) requires further consideration.

Conclusion—The few drugs displaying oral flip-flop kinetics in humans are predominantly BDDCS Classes 3 and 4. New molecular entities predicted to be BDDCS Classes 3 and 4 could be liable to exhibit flip-flop kinetics when the elimination half life is short and should be suspected to be substrates for intestinal transporters.

Keywords

BDDCS; flip-flop pharmacokinetics; half-life; oral drug absorption; transporters

Introduction

Accurate prediction of *in vivo* pharmacokinetics from *in vitro* measurements is an ongoing goal in the field of pharmaceutical sciences and was a primary incentive in the establishment by Amidon and colleagues[1] of the Biopharmaceutics Classification System (BCS). Wu and

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Benet [2] built upon the BCS by modifying it to include information concerning drug elimination, and thus created the Biopharmaceutics Drug Disposition Classification System (BDDCS; Figure 1) to aid in predicting *in vivo* drug disposition by identifying the role of drug transporters, here presented with respect to effects in the intestine, as reviewed by Shugarts and Benet [3]. The BDDCS gives scientists and clinicians a tool for predicting drug disposition and drug-drug interaction characteristics very early in development and with little additional expense. This paper is dedicated to Professor Amidon in recognition of his outstanding and seminal contributions to the pharmaceutical sciences. It would not have been possible to conceive of the BDDCS[2], without his prefatory insightful development of BCS[1].

Gastrointestinal absorption is generally faster than elimination for most immediate-release, orally dosed drugs. However, there are exceptions characterized as flip-flop pharmacokinetics, in which the rate of absorption of a drug is slower than its rate of elimination. It is termed “flip-flop” because the absorption is the limiting process for elimination, since a drug cannot be cleared from the system any faster than it enters into that system. It follows that observing an increased terminal elimination half-life following oral (p.o.) dosing of a drug, as compared to its intravenous (i.v.) half-life, is indicative of flip-flop pharmacokinetics. That is, while the ratio of a drug's absorption half-life to its elimination half-life ($t_{1/2,abs}/t_{1/2,elim}$) is usually less than one, in the case of flip-flop kinetics the ratio is greater than one. In 2011, Yáñez et al. [4] published an extensive review of flip-flop pharmacokinetics, identifying 12 drugs exhibiting flip-flop pharmacokinetics following immediate release oral dosing.

It is hypothesized here that drugs exhibiting poor intestinal membrane permeability rate would be those most likely to display flip-flop kinetics, as also noted by Yáñez et al.[4] Poorly permeable drugs generally have a low oil-to-water partition coefficient and are classified as BDDCS Classes 3 and 4, which are poorly metabolized. This report describes nineteen drugs that display flip-flop kinetics and are poorly metabolized, although one of these poorly metabolized drugs displays a very weak flip-flop profile. These drugs are all associated with Classes 3 and 4 of the BDDCS. Based on these classifications, the BDDCS predicts that absorptive (uptake) transporters may play an important role in the gastrointestinal absorption of Class 3 and 4 drugs (Figure 1). Here we suggest that *in vitro* measures of permeability rate and extent of metabolism will predict whether or not a drug would be likely to display flip-flop kinetics *in vivo*.

Methods

Drugs described in the literature as displaying flip-flop kinetics after oral dosing of immediate-release formulations in mammals (humans, monkeys, horses, rats or rabbits) were identified in a survey of previously reported pharmacokinetic studies. Searches using the term “flip-flop [or flip flop] kinetics [and pharmacokinetics]” were performed in both PubMed, Web of Science, via various internet searches (e.g. Google) and reexaminations of specific drug categories as will be described. The search results were then gleaned to identify reports of flip-flop drugs and their respective i.v. and p.o. half-lives. Studies investigating controlled release formulations, prodrugs or drugs administered via non-oral

delivery sites (e.g. intramuscular, inhalation, etc.) were excluded from consideration. Close to 200 studies identifying flip-flop pharmacokinetics were found via the search processes utilized, with the overwhelming majority related to formulations developed to achieve flip-flop pharmacokinetics for drugs with short half-lives. For example, a recent publication reports flip-flop kinetics for the Class 1 drug mycophenolate in transplant patients for an enteric-coated formulation [5]. Similarly, drugs with non-enzymatically catalyzed metabolism (e.g. thalidomide [6]) or drugs reported to display flip-flop kinetics under conditions of decreased intestinal motility that would affect absorption kinetics were also excluded (e.g. cephradine [7] or dabigatran etexilate [8,9]). Two additional drugs were excluded due to a lack of corroborating evidence in the literature: a report of possible flip-flop kinetics of etoposide in children was ambiguous [10]; a single report of the i.v. half-life of vildagliptin in humans [11] was within the range of p.o. half-lives reported in other human studies [12,13], and in addition, studies with vildagliptin in rats clearly demonstrated a lack of a flip-flop phenomenon [14].

Where available, the reported terminal half-life after p.o. dosing of a drug was compared to the elimination half-life after i.v. dosing, and a ratio was calculated for each. Drugs were then classified into the BDDCS based on solubility and extent of metabolism following the tabulation of Benet et al. [15]. A drug is said to be highly soluble in both BCS and BDDCS when its highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1-7.5 at 37°C [2]. Drugs were classified as highly metabolized if metabolism accounts for at least 60% of its elimination [15]. Of the 22 drugs found to exhibit flip-flop kinetics, 13 had a published BDDCS classification [15]. The remaining nine were classified based on the above criteria. Further searches of the literature were done to identify which of these drugs were known substrates of the uptake and efflux transporters expressed on the intestinal lumen and liver.

Results

Acamprosate, amoxicillin, ampicillin, calcium dosbesilate, carbovir, carvedilol, cefuroxime, cephalexin, fexofenadine, florfenicol, furosemide, levovirin, meclofenamic acid, metformin, nitrofurantoin, pravastatin, rebamipide, sapropterin, xamoterol, zanamivir and zidovudine are reported to display flip-flop kinetics, and nedocromil is reported to show a weak trend toward flip-flop kinetics (Table 1). Each of these drugs, except for carvedilol, meclofenamic acid and sapropterin, is eliminated primarily through excretion (i.e. poorly metabolized) and thus is assigned to Classes 3 or 4 of the BDDCS. Interestingly, zidovudine displays flip-flop kinetics in rats [16], where it is poorly metabolized (20-30 % metabolized [17-19], as compared to both monkeys [19,20] and humans [19,21,22] in which zidovudine displays normal kinetics and is extensively metabolized (60-75 % metabolized).

In the majority of cases presented in Table 1, the slow absorption process after an oral dose had a very obvious impact on pharmacokinetics and resulted in an observed terminal half-life that was longer by about two-fold or greater as compared to the i.v. dose elimination half-life. One clear exception was nedocromil, for which the flip-flop trend was weak and the absorption half-life to elimination half-life ratio was closer to one (Table 1). Notably, nedocromil has an inherently longer elimination half-life (13.8 h) than any of the other drugs

(0.3 – 7.7 h) that displayed convincing flip-flop kinetics. Two BDDCS Class 2 drugs[23-25] and one Class 1 drug[26] are reported to exhibit flip-flop pharmacokinetics.

Classification into the BDDCS helps to predict whether uptake and/or efflux transporters in the gut will play a role in the absorption of a drug [2,3] (Figure 1). The effects of transporters on the absorption of Class 1 compounds are negligible. For Class 2 compounds, the effects of efflux transporters are expected to dominate in the gut. The BDDCS predicts that absorptive transporter effects will predominate for Class 3 drugs, although efflux transporters in the gut may potentially modulate their disposition. For Class 4 drugs, the BDDCS predicts that the drug's disposition is likely to be to be affected by both absorptive and efflux transporters. Eighteen of the 21 drugs (omitting zidovudine) with flip-flop kinetics identified herein were poorly metabolized and thus classified as either Class 3 or 4. We recently reviewed intestinal drug transporters [27] and only half of the drugs exhibiting flip-flop kinetics have been previously shown to be substrates for at least one uptake and/or efflux transporter (not limited to intestinal transporters) that may play an important role in their pharmacokinetics (Table 2). When the drug is listed as a substrate in the UCSF-FDA Transportal database [28], this reference will provide primary reference sources.

Discussion

There are currently two major drug classification systems in use, the BCS and the BDDCS, which are based on the solubility and nominally the permeability of a drug. The BCS was developed to allow waiver of *in vivo* bioequivalence studies for highly soluble, highly permeable drugs, where rapid dissolution of immediate release dosage forms could be established [1,29]. However, as pointed out by Benet and Larregieu[30], the definitive criteria for assignment of Class 1 BCS is ≥ 90% absorption, and, in fact, a number of poor permeability rate drugs relative to metoprolol (e.g., cefadroxil, cephradine, levofloxacin, loracarbef, ofloxacin, pregabalin, and sotalol) showing ≥ 90% absorption are assigned to BCS Class 1[31]. In contrast, BDDCS was developed to predict drug disposition based on solubility and permeability rate, with the recognition that high permeability rate compounds were eliminated primarily by metabolism, while poor permeability rate drugs were eliminated by renal and biliary excretion of unchanged drug [2]. A strength of the BDDCS for predicting disposition including drug absorption and flip-flop kinetics lies in the ability to easily obtain values for extent of metabolism that are definitive, reliable and generally consistent from study to study. Alternatively, we have recently shown that in vitro measurements of permeability rate predict BDDCS Class 3 and 4 poor metabolism with 85.6±13.1% accuracy, which is better than utilizing in vitro permeability measurements to predict BDDCS Class 1 and 2 extensive metabolism at 74±7%[32] . In the current report, all but three of the drugs found to display flip-flop kinetics were poorly metabolized and thus associated with Classes 3 and 4 of the BDDCS. Zidovudine is a particularly interesting example. It is classified as BDDCS Class 1 for its extensive metabolism in humans, in whom it lacks flip-flop kinetics; however, zidovudine is BDDCS Class 3 in rats in which it is poorly metabolized and displays flip-flop kinetics[16,22].

One might expect that flip-flop kinetics would be observed with Class 2 drugs exhibiting poor solubility and/or extensive biliary recycling. However, neither we nor Yáñez et al. [4]

were able to identify any BDDCS Class 2 compounds that exhibited flip-flop kinetics in humans except carvedilol [23]. Here, in 20 healthy subjects the carvedilol i.v. half-life was 2.4 h, while the terminal half-life was 4.3 h for a 50 mg suspension, and 7.1 h and 6.4 h for a 25mg and 50 mg capsule, respectively [23]. It appears here that dissolution of this poorly soluble drug yielded the flip-flop kinetics for the suspension, with disintegration of the capsule (or dissolution of unwetted particles) causing the further terminal half-life increase. As noted in Table 1, an additional BDDCS Class 2 drug, meclofenamic acid, was found to exhibit flip-flop kinetics in horses [24,25]. As with the great majority of the drugs in Table 1, meclofenamic acid exhibits a rapid i.v. half-life, 1.4 hr. Meclofenamic acid would not be expected to exhibit flip-flop kinetics in humans since the package insert indicates that following oral dosing in ten subjects the mean elimination half-life was 1.3 hr, ranging from 0.8 to 2.1 hr.

As we had expected more Class 2 poorly soluble drugs to exhibit flip-flop pharmacokinetics, we examined studies for the 60 Class2 drugs listed by Benet et al.[15] with the highest dose numbers where oral and iv data are available without finding additional drugs to add to our list. We recognize that this is a very small subset of potential studies to examine. In the BDDCS classification[15], 230 Class 2 drugs are dosed orally, with each drug probably studied in 2 to 4 animal species plus humans. Thus, approximately 500 to 900 studies could be investigated outside of those identified as exhibiting flip-flop pharmacokinetics. Similarly 188 Class 3 and 4 orally dosed drugs may be found in the compilation[15]. Of these 188 drugs, we were able to identify 113 compounds where bioavailability following oral and iv dosing was reported in the Goodman and Gilman Pharmacokinetic Data compilations (7th through 12th editions). One of these drugs, zanamivir, exhibited slower oral absorption than elimination that was not identified as flip-flop pharmacokinetics in the publication[34]. We had previously identified zanamivir as exhibiting flip-flop pharmacokinetics following inhalation and intranasal administration, but did not identify the oral dosing data, and no oral dosage form of this drug had been approved (or submitted for approval), but we have included zanamivir in our listing in Table 1. Following identification of zanamivir, we carefully reviewed other drugs approved for inhalation or nasal administration. It is possible that albuterol may exhibit flip-flop pharmacokinetics following oral dosing[35], but our confidence in the report is not sufficient to list it here. We believe that the other two inhalation Class 3 and 4 drugs listed in Benet et al. [15], ipratropium and terbutaline, do not exhibit flip-flop pharmacokinetics.

During the review process for this paper flip-flop pharmacokinetics was reported for the drug sapropentin dihydrochloride in infants and young children with phenylketonuria[26]. Sapropentin dihydrochloride is a synthetic preparation of the naturally occurring phenylalanine hydroxylase cofactor tetrahydrobiopterin (BH4). We have listed the drug as BDDCS Class 1 because it is dehydrated by the enzyme PCD/DCoH (pterin-4a-carbinolamine dehydratase/dimerization cofactor of hepatocyte nuclear factor 1α)[33]. However, the body regenerates BH4 in vivo and the major route of elimination in humans is via the bile. Thus, in fact, because of the regeneration process, sapropentin dihydrochloride might be considered to have BDDCS Class 3 characteristics. However, as noted in Table 2 transporter effects on sapropentin (or BH4) have not been identified.

The current findings describe a further benefit of employing the BDDCS early in drug development. It is proposed that Class 3 and 4 drugs are primarily susceptible to flip-flop kinetics in humans, and the data suggest that such disposition is likely to be most apparent and a more important consideration for drugs with relatively short half-lives. One would like to know whether a drug exhibits flip-flop pharmacokinetics so as to be able to define the rate limiting step in drug elimination, so as to be able to predict potential drug interactions and the potential liability for toxicity-lack of efficacy outcomes.

Given that transit through the small intestine takes only a few hours following gastric emptying[36], the presence of a flip-flop phenomenon for immediate-release drugs would intuitively only be possible for drugs with half-lives not exceeding their gastrointestinal transit time. Additionally, classification as BDDCS Class 3 or 4 has implications for both drug-drug interactions as well as pharmacogenetics. In the former case, concomitant administration of another drug that affects the expression or function of a given transporter or enzyme may alter the pharmacokinetics of the drug of interest and potentially result in drug concentrations in either subtherapeutic or toxic ranges. In the latter situation, the natural variation of transporter expression or function also has the potential to affect a drug's disposition. For example, polymorphisms in OCT1 affect the pharmacokinetics of metformin in humans[37]. Thus, use of the BDDCS during early-stage development of novel drugs will help to identify those drugs that may encounter important transporter effects that require more directed characterization of their disposition.

Although flip-flop pharmacokinetics is a topic found in almost all pharmacokinetics textbooks and a topic of presentation in courses taught both in academia and in short courses taught to industrial scientists, there are very few drugs that inherently exhibit slower oral absorption than elimination (versus many controlled release drug products designed to achieve this phenomenon). This was found by Yáñez et al.[4] and in the review here. In fact, of the 698 orally dosed drugs examined by Benet et al.[15], only 9 are here documented to exhibit flip-flop pharmacokinetics in humans.

In summary, this report demonstrates that poorly metabolized drugs in BDDCS Classes 3 and 4 are associated with flip-flop kinetics in cases where the drugs have relatively short half-lives. Furthermore, absorptive and efflux transporters may potentially play important roles in the disposition of BDDCS Class 3 and 4 drugs. It might be expected that poorly soluble Class 2 drugs should also exhibit flip-flop kinetics where absorption is limited by dissolution, although only one example was identified. The implications of these findings are that simple *in vitro* measures of solubility and permeability rate can be used with the BDDCS early in development in order to predict whether or not flip-flop pharmacokinetics might occur (although few drugs would actually be expected to do so) and gut transporters are likely to influence the *in vivo* pharmacokinetic behavior of a new molecular entity. Thus, BDDCS classification helps to identify compounds early on for which increased characterization of transporter interactions may be necessary for the purpose of predicting potential drug-drug interactions including transporter-enzyme interplay, as well as assessing the potential importance of pharmacogenetic variability in a population.

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Abbreviations

BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BDDCS	Biopharmaceutics Drug Disposition Classification System
CNT	tetrahydrobioterin
BH4	concentrative nucleoside transporter
ENT	equilibrative nucleoside transporter
FDA	Food and Drug Administration
i.v	intravenous
MATE	multi-antimicrobial extrusion protein
MCT	monocarboxylate transporter
MDR	multidrug resistance transporter
MRP	multidrug resistance protein
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
OCTN	organic cation transporters novel
PEPT	peptide transporter
PMAT	plasma membrane monamine transporter
p.o	*per os*
UCSF	University of California, San Francisco

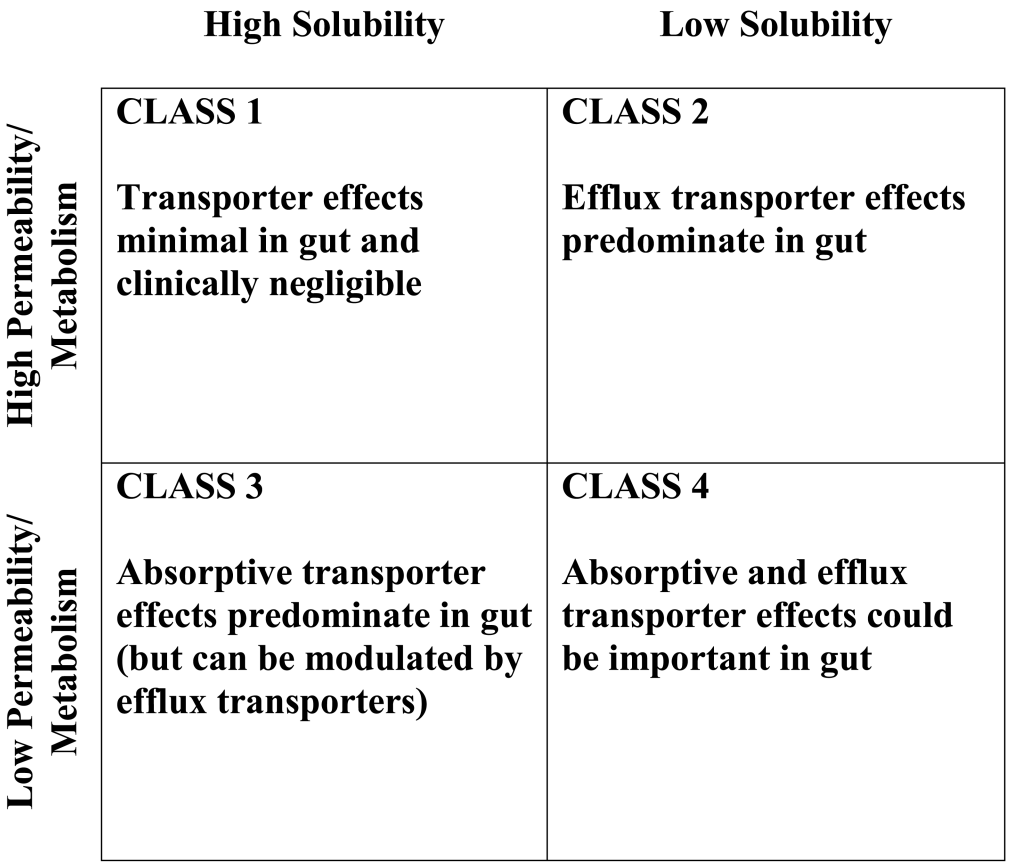

Figure 1. The Biophamaceutics Drug Disposition Classification System predicts the effects of transporters on drug absorption in the gut

Table 1

Drugs Displaying Flip-Flop Kinetics

Drug	BDDCS Class	$t_{1/2, i.v.}$ (h)	$t_{1/2, p.o.}$ (h)	$t_{1/2, p.o.}/t_{1/2, i.v.}$ ratio	Reference
Acamprosate	3	0.32	1.87	5.8 (rat)	[38,39]
		3.2	32.7	10.2 (human)	
Amoxicillin	3	1.31	2.62	2.0 (human)	[40]
Ampicillin	3	0.78	2.35-3.24	> 3.0 (human)	[41]
Calcium dobesilate	3	1.54	2.57	1.7 (human)	[42]
Carbovir	4	0.35	1.35	3.9 (rat)	[43,44]
Carvedilol	2	2.4	6.4 (capsule)4.3 (suspension)	2.7 (human)1.8 (human)	[23]
Cefuroxime	3	1.64	2.72	1.7 (rat)	[45]
Cephalexin	3	1.4	Reported flip-flop	Reported flip-flop (rat)	[46]
Fexofenadine	3	2.4	5.0	2.1 (horse)	[47]
		3.7	6.6	1.8 (monkey)	
		Unknown	Varies	Reported flip-flop (human)	
Florfenicol	3	1.7	4.8	2.8 (rabbit)	[48]
Furosemide	4	2.8	4.9	1.8 (human)	[49]
Levovirin	3	3.5	12.2	3.5 (monkey)	[50]
		1.5	4.5	3.0 (rat)	
		3.7	4.1	1.1 (dog)	
Meclofenamic acid	2	1.4	3.0	2.1 (horse)	[24,25]
Metformin	3	1.7	6.9	4.1 (human)	[51,52]
Nedocromil	3	13.8	15.9	1.2 (human)	[53]
Nitrofurantoin	4	0.25	0.63	2.5 (rabbit)	[54]
Pravastatin	3	0.78	1.77	2.3 (human)	[55]
Rebamipide	4	0.4	5.4	13.5 (rat)	[56]
Sapropterin	1	0.78	2.95	3.8 (human)	[26]
Xamoterol	3	7.7	16	2.1 (human)	[57]
Zanamivir	3	1.67	3.3	2.0 (human)	[34]

Drug	BDDCS Class	$t_{1/2, i.v.}$ (h)	$t_{1/2, p.o.}$ (h)	$t_{1/2, p.o.}/t_{1/2, i.v.}$ ratio	Reference
Zidovudine	3	1.6	3 to 4	2.2 (rat)	16-22
	1	1.14	1.65	1.4 (monkey)	
		1.1	1.0	< 1 (human)	

Table 2
Flip-Flop Drugs Are Known Substrates For Transporters

Drug	Gut and liver transporters		Reference
	Uptake	Efflux	
Acamprosate	--	--	
Amoxicillin	PEPT1, PEPT2	--	28
Ampicillin	PEPT1, PEPT2	MRP4	58,59
Calcium dobesilate	--	--	
Carbovir	Nucleoside, nucleobase	--	60
Carvedilol	--	--	
Cefuroxime	PEPT1, PEPT2	--	58
Cephalexin	PEPT1, OCTs	MATEs	28
Fexofenadine	OATP1A2, OATP2B1, OATP1B3	BCRP, MDR1, MRP2, MRP3	28
Florfenical	--	--	
Furosemide	OAT3	BCRP, MRP2, MRP4	28,59,61,62
Levovirin	--	--	
Meclofenamic acid	--	--	
Metformin	OCT1, OCT2, OCT3, PMAT	MATE1, MATE2K	28,63
Nedocromil	--	--	
Nitrofurantoin	--		
Pravastatin	MCT1, OATP1B1, OATP2B1, OAT3, OAT4	MRP2, MRP4, MDR1	28,59,64-66
Rebamipide	--	MRP4	59
Sapropterin	--	--	
Xamoterol	--	--	
Zanamivir	--	--	
Zidovudine	CNT1, ENT2, OCTN2, OAT1, OAT2, OAT3, OAT4	BCRP, MDR1, MRP4, MRP5	28,67-72