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POTENT INHIBITORS OF HUMAN ORGANIC ANION TRANSPORTERS 1 AND 3 FROM CLINICAL DRUG LIBRARIES: DISCOVERY AND MOLECULAR CHARACTERIZATION

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Abstract

Transporter-mediated drug-drug interactions in the kidney dramatically influence the pharmacokinetics and other clinical effects of drugs. Human organic anion transporters 1 (hOAT1) and 3 (hOAT3) are the major transporters in the basolateral membrane of kidney proximal tubules, mediating the rate-limiting step in the elimination of a broad spectrum of drugs. In the present study, we screened two clinical drug libraries against hOAT1 and hOAT3. Of the 727 compounds screened, 92 compounds inhibited hOAT1 and 262 compounds inhibited hOAT3. When prioritized based on the peak unbound plasma concentrations of these compounds, three inhibitors for hOAT1 and seven inhibitors for hOAT3 were subsequently identified with high inhibitory potency (>95%). Computational analyses revealed that inhibitors and non-inhibitors can be differentiated from each other on the basis of several physico-chemical features, including: number of hydrogen-bond donors, number of rotatable bonds, and topological polar surface area (TPSA) for hOAT1; and molecular weight, number of hydrogen-bond donors and acceptors, TPSA, partition coefficient (Log $P_{7.4}$), and polarizability for hOAT3. Pharmacophore modeling identified two common structural features associated with inhibitors for hOAT1 and hOAT3, viz., an anionic hydrogen-bond acceptor atom, and an aromatic center separated by ~5.7 Å. Such model provides mechanistic insights for predicting new OAT inhibitors.

Keywords

Drug transporter; Inhibitor; Drug–drug interactions; High-throughput screening; Pharmacophore modeling

Introduction

The organic anion transporter (OAT) family mediates the body disposition of a diverse array of environmental toxins and clinically important drugs, including anti-HIV therapeutics, anti-cancer drugs, antibiotics, anti-hypertensive, and anti-inflammatories^{1–5}. Therefore, understanding the structural prerequisites of ligands for these transporters bears profound clinical significance.

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Ten OATs have been cloned, and their expressions identified in distinct tissues and cell membranes. In the kidney, OAT1 and OAT3 utilize a tertiary transport mechanism to move organic anions across the basolateral membrane into the proximal tubule cells for subsequent exit across the apical membrane into the urine for elimination. Through this tertiary transport mechanism, Na^+/K^+ -ATPase maintains an inwardly directed (blood-to-cell) Na^+ gradient. The Na^+ gradient then drives a sodium dicarboxylate cotransporter, sustaining an outwardly directed dicarboxylate gradient that is utilized by a dicarboxylate/organic anion exchanger, namely OAT, to move the organic anion substrate into the cell. This cascade of events indirectly links organic anion transport to metabolic energy and the Na^+ gradient, allowing the entry of a negatively charged substrate against both its chemical concentration gradient and the transmembrane electrical potential of the cell ¹⁻⁵.

All of the cloned OATs share several common structural features including 12 transmembrane domains flanked by intracellular amino- and carboxyl termini; multiple glycosylation sites localized in the first extracellular loop between transmembrane domains 1 and 2; and multiple potential phosphorylation sites present in the intracellular loop between transmembrane domains 6 and 7 and in the carboxyl terminus. Studies by our laboratory on the structure-function relationship of OATs revealed that glycosylation is necessary for the targeting of these transporters to the plasma membrane ⁶.

One prominent feature of the OAT system is its interaction with and transport of a wide variety of clinically important anionic drugs¹⁻⁵, including β -lactam antibiotics, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), anti-HIV therapeutics, anti-cancer drugs, and inhibitors of angiotensin-converting enzymes. As a consequence of the multi-specific substrate recognition of the transporter, drug-drug interactions can take place at the transporter molecules. Drugs coexisting in the plasma may compete for the transporter processes, thus mutually influencing each other's pharmacological and toxicological profile. Such drug-drug interactions are an important consideration in drug development and therapy. In fact, in the newly published FDA guidance for industry on drug interaction studies, it was suggested that all investigational drugs should be evaluated *in vitro* to determine whether they are a substrate of OAT1, OAT3 or the organic cation transporter 2 (OCT2) when renal active secretion contributes to most of its elimination ⁷.

In the present study, we employed an integrated strategy that comprised fluorescent screening and computational modeling to identify hOAT1 and hOAT3 inhibitors from two clinical drug libraries consisting of a total 727 drugs. This study has contributed to our understanding of the common molecular features which are deemed necessary for inhibition of hOAT1 and hOAT3.

Materials and Methods

The NIH Clinical Collection (NCC) and NIH Clinical Collection 2 (NCC2) were acquired from Evotec CA, USA. 6-carboxyfluorescein (6-CF) was acquired from Sigma-Aldrich, USA. All compounds unless specified otherwise were acquired from Sigma-Aldrich with an analytical grade of at least 95% purity.

Cell culture

Monkey kidney COS-7 cells stably expressing human hOAT1 and hOAT3 were previously established in our lab ^{8, 9}. Cells were cultured in Dulbecco's modified Eagle's medium (Invitrogen, USA) supplemented with 10% fetal bovine serum and 100 unit/ml penicillin, 100 $\mu\text{g}/\text{ml}$ streptomycin and 0.5 mg/ml geneticin (G418; Invitrogen, Carlsbad, CA) at 37 °C in a humidified incubator with 5% CO_2 .

Fluorescence uptake assay

Cells ($\sim 5 \times 10^4$ /well) were seeded in black wall poly-D-lysine-coated 96 well plates (COSTAR®, Corning Inc, USA) 24 hrs prior to experiments. Uptake was initiated by adding PBS supplemented with 1 mM of $MgCl_2$ and 1 mM of $CaCl_2$ containing 20 μM fluorescent substrate 6-CF in the presence of other drugs from the drug libraries, and incubating at room temperature for 12 min. The uptake was stopped by washing cells with ice cold PBS. Cells were then lyzed with 0.2 N NaOH for 1 hr. All compounds were measured in duplicate or triplicate. The intensity of accumulated 6-CF inside the cells was measured using an FLx800 microplate fluorescence reader (Bio-Tek instrument Inc., USA), with excitation and emission wavelengths at 485 and 560 nm, respectively.

Transport kinetics were characterized by measuring the uptake of increasing concentration of 6-CF in COS-7 cells stably expressing hOAT1 and hOAT3 and subtracting the background values from parental COS-7 cells. The uptake value was fitted to the Michaelis-Menten equation $V = V_{max} * S / (K_m + S)$ where V_{max} is the maximum transport rate, K_m is the substrate concentration resulting in half-maximal uptake rate, and S is the concentration of 6-CF, using GraphPad Prism software (GraphPad Software Inc, USA). The Z' assay factor was calculated according to the equation $Z' = 1 - 3(\delta_{sample} + \delta_{control}) / (\mu_{sample} - \mu_{control})$ where δ and μ are the standard deviation and the mean, respectively¹⁰.

Transporter inhibition assay

The half-maximal inhibitory concentration (IC_{50}) was estimated from the inhibition screening measurements as $V = V_0 / [1 + (I/IC_{50})]^n$ ¹¹, where V and V_0 are the activity with and without inhibitor, respectively, and I is the inhibitor concentration of 50 μM for hOAT1 and 20 μM for hOAT3. Based on above equation, for hOAT1 ($I=50 \mu M$), the estimated IC_{50} for the compound that inhibits the activity of the transporter more than 95% (>95% inhibition) should be lower than 2.63 μM ; while for hOAT3 ($I=20 \mu M$), the estimated IC_{50} for the compound that inhibits the activity of the transporter more than 95% should be not more than 1.10 μM . Inhibitors with IC_{50} meeting these cutoff values would be considered as highly potent inhibitors. The estimated IC_{50} values were compared with plasma concentration (C_{max}) data of each tested chemical collected from the literature. This estimated IC_{50} was further confirmed by experimental measurements of IC_{50} . Experimental IC_{50} values were measured as the uptake of 6-CF in the presence of increasing concentration of inhibitors (0.5 μM to 500 μM). Data were fit using nonlinear regression to Equation 1, where V and V_0 are the 6-CF uptake rate in the presence and absence of the inhibitor, respectively. I is the inhibitor concentration, and n is the slope.

$$V = V_0 / [1 + (I/IC_{50})^n] \quad (\text{Equation 1})$$

IC_{50} was converted to K_i by Equation 2 before conversion to the $-\log$ value (pK_i), where C is the substrate concentration and K_m is the Michaelis constant.

$$K_i = \frac{IC_{50}}{[1 + (\frac{C}{K_m})]} \quad (\text{Equation 2})$$

Molecular descriptor generation

The descriptors, specifically the molecular weight, volume, number of rotatable bonds, Log $P_{7.4}$, TPSA, molecular polarizability, number of hydrogen-bond donors and number of

hydrogen-bond acceptors, were calculated using the Chemaxon JChem package (ChemAxon, USA).

Pharmacophore construction

The Molecular Operating System (MOE, Chemical Computing Group, Montreal, Canada) was used for the identification and evaluation of chemical features of sixteen highly potent OAT inhibitors with IC₅₀ values determined by experiment (Experimental IC₅₀). MOE automatically detects pharmacophoric features and generates annotations for each ligand. Then common features among structurally diverse ligands were identified through three steps: (i) Each compound was energy minimized to the putative global low-energy conformation in the following manner using MOE *energy minimize* module. Using the standard Tripos molecular force field with a dielectric constant of $\epsilon=4.0$, molecules were first geometry optimized to the nearest local minimum energy conformation until an energy difference of 0.001 kcal/mol between successive iterations was achieved. All rotatable (i.e., single) bonds were then systematically searched in 10° increments and, after setting the torsion angles to the lowest-energy conformer among those scanned, the molecule was geometry optimized a final time; (ii) Pharmacophore sites were identified by molecular alignment using the unified scheme in the MOE *pharmacophore* module. (iii) Common pharmacophores were found by distance-based inter-site grouping.

Results

Establishment of fluorescent probe for high-throughput screening (HTS) assay

The compound 6-CF was previously used as a fluorescent tracer for mouse OAT-mediated transport in *Xenopus* oocytes¹². In the present study, uptake of 6-CF into hOAT1- and hOAT3-expressing COS-7 cells, measured fluorometrically, was linear up to 30 min and gave a K_m of 12.7 μ M for hOAT1 and 7.24 μ M for hOAT3 (Fig. 1). We then evaluated Z' factor, a parameter to determine the suitability of an assay for HTS¹⁰. An excellent assay is indicated by the condition $1 - Z' \text{ factor} = 0.5$. The Z' factor for hOAT1 and hOAT3 were 0.70 and 0.66, respectively, indicating excellent assay performance for HTS.

Identification of hOAT1 and hOAT3 inhibitors from drug libraries

The NIH Clinical Collection (NCC) and NIH Clinical Collection 2 (NCC2) drug libraries used for HTS consisted respectively of 446 and 281 small molecules (727 total) approved for clinical use or having a history of use in human clinical trials. The clinically tested compounds in the NCC and NCC2 libraries are highly drug-like with known safety profiles. At the indicated concentrations, 92 compounds resulted in 50 % decrease in hOAT1-mediated 6-CF transport, whereas 262 compounds resulted in 50 % decrease in hOAT3-mediated 6-CF transport (Fig. 2). All of the 92 hOAT1 inhibitors were also inhibitors for hOAT3 but with a different potency. Among the 262 inhibitors for hOAT3, 8 compounds were specific for hOAT3 (Table 1), i.e., they lacked appreciable inhibitory activity for hOAT1. For example, stiripentol inhibited hOAT3 with an IC₅₀ of $27.6 \pm 1.28 \mu$ M, but it barely had any effect on hOAT1 (not shown). These inhibitors for hOAT1 and hOAT3 included classes of anti-inflammatory, antiseptic/anti-infection, antineoplastic, steroid hormones, cardiovascular, antilipemic, CNS, gastrointestinal, respiratory and reproductive control drugs.

Among those inhibitors retrieved from the initial screening, we selected clinically relevant inhibitors for hOAT1 and hOAT3 based on the criteria that the ratio of their peak plasma concentrations (C_{max}) to their estimated IC₅₀ (Eq. 1) exceeded 0.1⁷ at typical clinical doses and they were commercially available. For hOAT1, 35 of the 92 inhibitors were selected with ten compounds showing high inhibition potency (>95% inhibition of hOAT1 activity in

transporter inhibition assay, Table 2). For hOAT3, 73 of the 262 inhibitors were selected with fourteen showing high inhibition potency (>95% inhibition of hOAT3 activity in transporter inhibition assay, Table 3).

We further increased the stringency of our selection criteria by incorporation of peak unbound plasma concentration of drugs since, for drugs tightly bound to plasma proteins, the free concentration in plasma is a better estimate of the drug level interfering with OAT transport function. Further screening using the peak unbound plasma concentration yielded three inhibitors of hOAT1 (Table 4) and seven inhibitors of hOAT3 (Table 5) with potency >95% inhibition.

Comparison of molecular characteristics between inhibitors and non-inhibitors

Next, we examined the distribution of calculated molecular features among inhibitors and non-inhibitors of hOAT1 or hOAT3 (Fig 3). The molecular descriptors of all the compounds in the library were first generated by the Chemaxon JChem package followed by frequency distribution analysis between inhibitors (from the initial screening, which resulted in >50% decrease in transport activity at indicated concentrations in Fig. 2 legend; 92 compounds for hOAT1 and 262 compounds for hOAT3) and non-inhibitors. For hOAT1, statistically significant differences ($p < 0.05$) were found in number of hydrogen-bond donors, number of rotatable bonds, and topological polar surface area (TPSA) (Fig. 3a). For hOAT3, statistically significant differences ($p < 0.05$) were found in molecular weight, number of hydrogen-bond donors and acceptors, TPSA, Log $P_{7.4}$, and molecular polarizability (Fig. 3b).

Structural alignment and pharmacophore prediction

In order to understand the structure–activity relationship of hOAT1 inhibition, we further performed pharmacophore analysis to identify the important common features of OAT inhibitors. Based on analysis of the sixteen inhibitors with > 95% inhibition potency (Table 2, Table 3, Fig. 4), we proposed a simple pharmacophore model to discriminate between OAT inhibitors and non-inhibitors. This two-point model has two structural features (one anionic hydrogen-bond acceptor atom, and an aromatic center) separated by ~5.7 Å (Fig. 5). Searching the collection of OAT non-inhibitors using the pharmacophore model produced no hits, thus attesting to the specificity of the model.

Discussion

Drug–drug interactions are one of the leading causes of drug withdrawals from the market. Although drug interactions with drug metabolizing enzymes have been extensively studied, transporter-mediated drug–drug interactions have attracted significant attention only recently. OAT1 and OAT3 are among several important transporters designated in the newly published FDA guidance for which drug–drug interactions should be evaluated during drug development⁷. In the present study, we analyzed the inhibition of hOAT1 and hOAT3 with the NCC and NCC2 collection of 727 clinically relevant compounds by high-throughput screening. Those compounds found to be potent hits (>95% inhibition of transporter activity) for hOAT1 or hOAT3 were subjected to computational analysis to gain insights into the biophysical features and structural requirements for inhibition of these transporters.

We evaluated the inhibition potential of these 727 test compounds with increasing stringencies. When the clinical peak unbound plasma concentrations were used, potency at >95% inhibition was exhibited by 3 compounds for hOAT1 and seven compounds for hOAT3, suggesting that concomitant administration of these drugs with other drugs might

pose a high risk of drug-drug interactions. Whether these inhibitors are translocated across the cell membrane through hOAT1 and hOAT3 will be the subject for future investigation.

Our computational analysis showed that the key molecular descriptors for inhibitors of hOAT1 and hOAT3 are quite broad. The number of H-bond donors, number of rotatable bonds, and TPSA were useful for discriminating between hOAT1 inhibitors and non-inhibitors, whereas molecular weight, number of H-bond donors and H-bond acceptors, TPSA, molecular polarizability and Log $P_{7.4}$ were useful for discriminating between hOAT3 inhibitors and non-inhibitors. Similar molecular features have been proposed in published reports for inhibitors of other transporters. For example, positive charge, lipophilicity, and hydrogen bond donors seem to play important roles for organic cation transporter 1 (OCT1)¹³, whereas charge, lipophilicity, molecular size, and flexibility were identified for organic cation transporter 2 (OCT2)¹⁴. Certain descriptors are more important for hOAT3 than for hOAT1. For example, molecular weight was statistically important for hOAT3, but not for hOAT1. It has been shown that the substrate binding regions for hOAT1 and hOAT3 are different¹⁵. Substrates with more bulky groups or larger volumes generally prefer to bind OAT3 rather than OAT1, an observation which may suggest why molecular weight (i.e., molecular size) is more important for hOAT3 inhibitors than for hOAT1 inhibitors. Nonetheless it seems that the potency of hOAT1 and hOAT3 inhibitors depends on contributions from all of these descriptors in some way rather than from a single dominant descriptor, since a statistically significant correlation was not found between any of these descriptors alone and inhibitor potency pKi (data not shown).

Our pharmacophore modeling deduced a two-point model that manifests two structural features (one anionic hydrogen-bond acceptor atom, and an aromatic center) separated by 5.7 Å. This structural characteristic is present among the high potent inhibitors for both hOAT1 and hOAT3, except Nitazoxanide (CID:41684) due to lack the anionic atom required to fit our model. However, its active metabolite and hydrolysis product Tizoxanide (CID: 394397) does contain a phenolic OH that may be sufficiently acidic to yield an anion and thereby satisfy our pharmacophore model (Fig. 5). The existence of the common pharmacophore features found in both hOAT1 and hOAT3 inhibitors might explain why inhibitors for hOAT1 also inhibit hOAT3-mediated transport and vice versa, although with different inhibitory potencies. Previous studies on pharmacophore models of most potent inhibitor drugs of OCT2 deduced a similar two-point pharmacophore consisting of a cationic site and a hydrophobic aromatic site separated by 5.0 Å¹⁴. Belonging to the same solute carrier family, OCT2 and OATs all share key structural features, such as twelve transmembrane domains. This may suggest the apparent high degree of similarity between their pharmacophore models. The anionic site in OAT inhibitors and the cationic site in OCT2 inhibitors are consistent with their respective substrate preference.

The significance of our studies is two-fold. First, inhibition of hOAT1 or hOAT3 by one of the drugs identified in the present study (Tables 1–5) may result in the accumulation of another drug in the system, leading to toxic effects. Second, such inhibition may increase the retention time of drugs in the blood, thus improving their therapeutic efficacy if a longer half-life is preferable.

In summary, the present study screened inhibitors for hOAT1 and hOAT3 against a collection of clinical relevant compounds including prescription drugs (viz., NCC and NCC2). The most potent inhibitors (>95% inhibition), especially when considered at their peak unbound plasma concentrations, likely pose the greatest risk of clinical drug-drug interactions. The key molecular descriptors and pharmacophore model presented here for hOAT1 and hOAT3 inhibitors may provide valuable information both for structure-based

drug design and for virtual screening of chemical databases in order to flag OAT1 and OAT3 inhibitors.

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Fig. 1. Concentration dependence of 6-CF uptake in hOAT1- and hOAT3- expressing cells
a. The hOAT1-mediated specific uptake was calculated by subtracting the nonspecific uptake in control cells from that in the cells expressing hOAT1. b. The hOAT3-mediated specific uptake was calculated by subtracting the nonspecific uptake in control cells from that in the cells expressing hOAT3.

Fig. 2. Inhibitors of hOAT1 and hOAT3 identified in a screen of 727 clinically tested drugs

a. Overview of the results from the screening of hOAT1 inhibition. The 92 compounds (at 50 μ M) resulting in at least 50% decreased uptake of 6-CF were classified as inhibitors (shaded in light gray and under the curve). Data were presented as the mean $\pm$ SD (samples in triplicate from one experiment). b. Overview of the results from the screening of hOAT3 inhibition. The 262 compounds (at 20 μ M) resulting in at least 50% decreased uptake of 6-CF were classified as inhibitors (shaded in light gray and under the curve). Data were presented as the mean $\pm$ SD (samples in triplicate from one experiment).

Fig. 3a

Fig. 3b

Fig. 3. Structural features of hOAT1 and hOAT3 inhibitors

a. Distribution of key physicochemical properties of hOAT1 inhibitors. b. Distribution of key physicochemical properties of hOAT3 inhibitors. The calculated descriptors (viz., TPSA, molecular weight, volume, number of rotatable bonds, Log P_{7.4}, molecular polarizability, number of hydrogen-bond donors and hydrogen-bond acceptors) were calculated using Chemaxon JChem package (ChemAxon, USA). The frequency distribution analysis was conducted between inhibitors and non-inhibitors by Graphpad prism 5.0. *P < 0.05 was considered significantly different, and n.s. stood for no significant difference.

<p>CID: 2161</p> <p>Amlexanox</p>	<p>CID: 4614</p> <p>Oxaprozin</p>	<p>CID: 41684</p> <p>Nitazoxanide</p>	<p>CID: 84003</p> <p>Ketorolac Tromethamine</p>
<p>CID: 65999</p> <p>Telmisartan</p>	<p>CID: 3749</p> <p>Irbesartan</p>	<p>CID: 60846</p> <p>Valsartan</p>	<p>CID: 9576744</p> <p>Parecoxib Na</p>
<p>CID: 3825</p> <p>Ketoprofen</p>	<p>CID: 3059</p> <p>Diflunisal</p>	<p>CID: 4044</p> <p>Mefenamic Acid</p>	<p>CID: 4038</p> <p>Meclofenamic Acid</p>
<p>CID: 5311309</p> <p>Nateglinide</p>	<p>CID: 60560</p> <p>Pioglitazone</p>	<p>CID: 6335412</p> <p>Balsalazide</p>	<p>CID: 3278</p> <p>Ethacrynic Acid</p>

Fig. 4.
Structures of inhibitors used in pharmacophore analysis.

Fig. 5. Pharmacophore model of hOAT1 and hOAT3 inhibitors

Two representative OAT inhibitors were mapped to the proposed pharmacophore model. The anionic and hydrogen-bond acceptor atom is displayed as cyan sphere and labeled F1:Ani &Acc, while the aromatic center is represented as a yellow sphere and labeled F2:Aro. Carbon atoms in the compound (CID: 84003) is colored in magenta and those in the compound (CID: 60560) is shown in gray. The other atoms in the compounds are colored by atom type (nitrogen: blue; oxygen: red; sulfur: yellow).

Table 1

hOAT3-specific Inhibitors

Stiripentol	Cortisol succinate	Demeclocycline
Penciclovir	Ornidazole	Benazepril
Chlorpropamide	Artesunate	

Table 2

Highly potent inhibitors for hOAT1 at peak plasma concentrations

Amlexanox	Telmisartan	Mefenamic Acid
Oxaprozin	Parecoxib Na	Meclofenamic Acid
Nitazoxanide	Ketoprofen	
Ketorolac Tromethamine	Diflunisal	

Table 3

Highly potent inhibitors for hOAT3 at peak plasma concentrations

Mefenamic Acid	Meclofenamic Acid	Pioglitazone
Oxaprozin	Nateglinide	Amlexanox
Ketorolac Tromethamine	Diffunisal	Nitazoxanide
Irbesartan	Valsartan	Telmisartan
Balsalazide	Ethacrynic Acid	

Table 4

Highly potent inhibitors for hOAT1 at peak unbound plasma concentrations

Compounds	IC50 in COS-7 cells (μM)	Cmax (μM)	Cmax Unbound (Cu.p) (μM)	Cu.p/IC50
Oxaprozin	0.891±0.292	501 ¹⁶	5.01 [*]	5.62
Mefenamic Acid	1.085±0.124	83.0 [*]	8.30 [*]	7.60
Ketorolac Tromethamine	0.653±0.130	9.50 ¹⁷	0.100 ¹⁷	0.150

^{*} Data comes from Dailymed.nlm.nih.gov

Table 5

Highly potent inhibitors for hOAT3 at peak unbound plasma concentrations

Compounds	IC50 in COS-7 cells (μM)	Cmax (μM)	Cmax Unbound (Cu.p) (μM)	Cu.p/IC50
Nateglinide	0.860±0.0953	18.0 ¹⁸	0.230 ¹⁹	0.270
Oxaprozin	0.870±0.0704	501 ¹⁶	5.01 [*]	5.76
Nitazoxanide	0.154±0.0711	31.2 [■]	0.0300 [■]	0.200
Valsartan	0.250±0.143	14.8 ²⁰	0.850 ²¹	3.47
Ethacrynic Acid	0.662±0.261	30.9 ²²	0.600 [▲]	0.910
Diflunisal	0.720±0.290	496 [■]	0.490 [■]	0.680
Mefenamic Acid	1.75±0.258	83.0 [*]	8.30 [*]	4.74

* Data comes from Dailymed.nlm.nih.gov

■ Data comes from Drug.com

▲ Data comes from Drugbank.ca