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„Chemical landscape of SLC-transporter ligands “

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Abstract

The big amount of different SLC-transporter, which count 458 transport proteins-belonging to 65 families, can be challenging for keeping an overview. While there are families which are already well researched, there are still many SLC families where we do not know much about them.

The aim of this work was to provide an overview on the ligand space interacting with SLC-transporter. This could lead the attention also to SLC-proteins which are not yet considered as important as others. Beyond, the way of looking at things may change, what always is a good start for new findings.

Working with big data, available in the ChEMBL-Database, requires a good software. In this case, KNIME was the suitable analytics platform. Starting the workflow with defining the targets and receiving over 86 000 molecules binding them, it was necessary to place some filter-nodes. Concentrating only on “small molecules” did not really decrease the number of molecules. For this reason, the focus was placed on “inhibitors”.

Another reduction option, after filtering out molecules which only bind but do not inhibit the targets, was to concentrate only on data where “pChEMBL-values” are available. The “PChEMBL-value” shows measures of half-maximal response/affinity/potency on a negative logarithmic scale. When filtering for this condition, it was also of interest to point out the different occurrence of SLC families when splitting into pChEMBL ranges.

Categorizing SLC-transporters in ways like this may show where further research could focus on, and if there are still SLC-proteins with inhibiting potential left.

Zusammenfassung

Es kann eine Herausforderung sein, bei der großen Menge an unterschiedlichen SLC-Transportern, von denen man derzeit 458 Transportproteine kennt, die 65 Familien untergeordnet sind, den Überblick zu behalten. Es gibt bereits sehr gut erforschte SLC-Bereiche, jedoch gibt es noch viele SLC-Familien, über die wir nicht viel wissen.
Ziel dieser Arbeit ist es, einen Überblick über den chemischen Raum der SLC-Liganden zu erarbeiten. Dies könnte die Aufmerksamkeit auch auf SLC-Proteine lenken, die noch als weniger wichtig empfunden werden als andere. Darüber hinaus kann sich die Sichtweise auf die umfangreiche SLC-Welt ändern, was ebenfalls ein guter Beginn sein kann neue Erkenntnisse zu gewinnen.
Die Arbeit mit Big Data, verfügbar in ChEMBL, erforderte eine gute Software. In diesem Fall war KNIME die geeignete analytische Plattform. Zu Beginn des Workflows wurden mit der Definition der Targets über 86.000 Molekülen erhalten, die diese binden. Die Konzentration nur auf „kleine Moleküle“ verringerte die Anzahl der Moleküle nicht signifikant. Aus diesem Grund lag der Fokus auf „Inhibitoren“.
Eine weitere Reduktionsmöglichkeit bestand darin, sich nach dem Herausfiltern von Molekülen, die die Targets lediglich binden, aber nicht inhibieren, sich nur auf Daten zu konzentrieren, bei denen „pChEMBL-Werte“ verfügbar sind. Der „PChEMBL-Wert“ zeigt Messungen der halbmaximalen Reaktion/Affinität/Potenz auf einer negativen logarithmischen Skala. Bei der Filterung nach dieser Bedingung war es auch von Interesse, auf das unterschiedliche Auftreten von SLC-Familien bei der Aufteilung in pChEMBL-Bereiche hinzuweisen.
Die Kategorisierung von SLC-Transportern auf diese Weise könnte zeigen, wo sich die weitere Forschung konzentrieren könnte und ob es noch SLC-Proteine mit Hemmpotenzial gibt.

Introduction

Definition of SLC transporter

Solute carrier transporters, together with ATP-binding cassette transporters, belong to the main transporter superfamilies. Whereas ABC transporters mainly function as efflux transporters, the SLC superfamily primarily regulate the uptake of molecules into cells.
Hydrophilic molecules, including charged molecules, are not able to diffuse across membranes on their own. They need channels, pumps or transporter to move in and out of cells.
SLC transporters, which are basically membrane-bound proteins, let pass substrates through various biological membranes. Substrates, which are transported, can either be nutrients, drugs, or other xenobiotics. Furthermore, the place of expression varies from family to family. Actually, SLC-transporter can be found anyplace in our body, preferentially in the epithelia of the liver, kidney, intestine and organs with barrier functions, such as the brain, testes and placenta. (Lawrence Lin, 2015) (1)

The classification of this about 65 families was based on their sequence similarity. To classify them even more precisely, the families are also divided into subfamilies. In total, 458 transporters have been identified by now. (Alexander SPH, 2019)(2)
To give a better overview, it is common to name these transporters on their substrates. The disadvantage is, that there are many SLC families which overlap in terms of which solutes they carry. To give an example: amino acids, which are needed for protein synthesis, are absorbed and reabsorbed by different transporter-families. SLC1, SLC3, SLC6, SLC7, SLC15, SLC16, SLC17, SLC32, SLC36, SLC38 and SLC43 carry amino acids across biological membranes. Many of the same transporter that are responsible for absorption of amino acids through the intestine into the body, are also responsible for the reabsorption of amino acids in the proximal tubules of the kidney, after they were filtered out of the bloodstream by the glomerulus.
Examples for Solute carrier-families that have this double responsibility are SLC2, SLC5 and SLC50. They absorb intestinal and reabsorb renal glucose. Furthermore, they manage the glucose uptake into neurons, erythrocytes, hepatocytes, and other cells. (Lawrence Lin, SLC Transporters as Therapeutic Targets: Emerging Oppurtunities, 2015)(3)

SLC related diseases

Pathways of nutrients and metabolites like glucose, vitamins and neurotransmitters play a major role in our metabolism and thus also in various diseases. SLC transporter function as “metabolic gate” wherefore the potential as drug targets is immense. Hyperglycemia, uricosuria, gout, cancer, and depression are diseases where scientists already have made progress while using SLC transporter as drug targets.
For an example, gliflozins, which are nowadays an indispensable part of diabetes mellitus type2 therapy, act by inhibiting sodium/glucose cotransporter 2 -better known as SGLT-2 inhibitors. SGLT-2 can also be named as SLC5A2.
Another well-known example is fluoxetine. Fluoxetine belongs to the class of selective serotonin reuptake inhibitors and is commonly used in the therapy of anxiety, obsessive compulsive disorder, and bulimia. The mechanism of action is the inhibition of SLC6A4, which is responsible for transporting the neurotransmitter serotonin from synaptic spaces into presynaptic neurons. (Yong Zhang, 2019)(4)

One of the best studied SLC-family is SLC22. SLC22 can be divided into six subfamilies: OAT (organic anion transporter), OAT-like, OAT-related, OCT (organic cation transporter), OCTN (organic cation/carnitine transporter), and OCT/OCTN-related.
SLC22 family members are present in almost every barrier membrane within the human body (blood-brain-, blood-testis, blood-cerebrospinal fluid -barrier, and various CNS cell types). Nevertheless, expression and function in kidney, liver and intestine has received the highest attention. (Raymond E. Lai, 2018)(5)
Mutations at transporters of the SLC22 family may cause specific diseases such as "primary systemic carnitine deficiency" or "idiopathic renal hypouricemia" or change drug absorption or excretion. (6)

SLC transporter gene polymorphism

Examples for polymorphism in transporter genes which can lead to diseases are the following: SLC22A4 and SLC22A5 are associated with inflammatory bowel disease; SLC2A9, SLC22A11 and SLC22A12, which are associated with gout and uric acid levels, as well as SLCO1B1 and SLCO1B3, which are associated with high bilirubin levels.
Polymorphisms in the genes of transporters that are involved in the hepatic bilirubin elimination pathway may lead to hyperbilirubinemia and jaundice.
In the past years, new findings of coherences between SLC polymorphisms and human diseases were made. To give some examples: a genetic polymorphism of SLC30A8, which encodes a pancreatic β-cell-specific zinc transporter, has been associated with diabetes; SLC14A1 variants, which encodes a urea transporter, have been associated with bladder cancer; polymorphisms at SLC4A7, which encodes a bicarbonate transporter, have been associated with abnormal blood pressure or with breast cancer. (3)
These SLC polymorphisms can lead to the assumption that with the help of drugs, by either inhibiting or increasing the function of Solute carriers, various changes in metabolism can be achieved.
As it can be seen, many findings were just made a few years ago and there is still plenty of space left for research. Within the past 10 years, 9 new SLC families have been identified and nearly 100 human SLC genes have been recognized. Methods which make crystal structures and molecular models of SLC transporters available, as well as SLC-knockout mice, are speeding up research. (3)

Aim of this work

The aim of this thesis was to give an overview of the big world of SLCs and their ligands. The focus was on small molecules which are inhibiting Solute carriers. While different SLC transporter, or even SLC families, have already been researched in detail, there are SLC families which have been disregarded. To recall the variety of solute carriers, it is important to provide an exhaustive overview. Even the way of looking at a topic in a different way can lead to new findings. Performing statistical analysis and representing the results graphically has the advantage of a neutral and detached point of view.

Methods

RESOLUTE

The groundwork for my further research was set by the RESOLUTE Consortium. "*RESOLUTE is a public-private partnership with 13 partners from academia and industry with an overarching goal: To trigger an escalation in the appreciation and intensity of research on solute carriers (SLCs) worldwide and to establish SLCs as a tractable target class for medical research and development*." (7) As the substrate and function of 30 percent of solute carriers is still unknown, universities, research institutes, SMEs, European Federation of Pharmaceutical Industries and Associations (EFPIA) are working together on new research output.

Daniela Digles, who is working as a post-doc in the Pharmacoinformatics Research Group of Gerhard Ecker, is involved in the RESOLUTE project and gave me the excel sheet with SLC-transporter with which I could start my work. Having a list of 446 SLC transporter as potential targets simplified the start of my thesis. 446 defined targets contained 431 SLC subfamilies which are associated to 65 families. For 15 defined targets, no SLC subfamilies have been identified yet. Since the list also contained the UniProt Accession-number, it was possible to connect these defined targets with associated information available in ChEMBL.

ChEMBL

The suitable database to obtain information about molecules which are binding to these defined targets was ChEMBL. "*ChEMBL is a manually curated database of bioactive molecules with drug-like properties. It brings together chemical, bioactivity and genomic data to aid the translation of genomic information into effective new drugs*. "(8)

ChEMBL version28, which is the current version I used, contains 14.554 targets, 2.105.464 distinct compounds, 18.635.916 activities and 81.544 publications. The big advantage of this source of data is, that it is freely available. In my case, another major plus is the amount of activity comments. The pChEMBL value, for example, was an important figure in my thesis.

On the one hand I had a clear table of targets. On the other hand, there was this enormous amount of data in ChEMBL. The next step was to connect the list of SLCs with existing data to get perspicuous output. As already mentioned, the UniProt Accession-number was existing for every SLC-transporter in the list I received from Daniela Digles. My task was to connect the UniProt Accession-number of previous defined targets with data available in ChEMBL. The perfect software doing this and, in addition, analyzing big data and building a reproducible workflow, was KNIME.

KNIME

„KNIME Analytics Platform is the open-source software for creating data science. Intuitive, open, and continuously integrating new developments, KNIME makes understanding data and designing data science workflows and reusable components accessible to everyone. “(9)

The aim in KNIME is to create a workflow, which in the end can be reproduced and helps to analyze, visualize, or extract data. Input of data can be done by different nodes and in different format. Searching for “Reader”-nodes in KNIME Hub, 330 results will be suggested. To name only a few, there is “Excel-Reader” which I was using, but also “SDF-/TDF-/PDB-/XLS-Reader. You can even start with “Workflow-Reader” and build new outputs. It is also possible to get data out of the internet and connect it with your local data. This enabled me to combine information from ChEMBL with my existing Excel-sheet. With KNIME Analytics Platform the possibilities are almost limitless. 4.054 nodes, 597 components, 6.138 workflows and 218 extensions are available. In the beginning, when downloading the software, not all nodes are present from the start. There is the option to download extensions, some are developed and maintained by KNIME itself, others by partners. There are also integrations with many open-source projects. It can be challenging at the beginning, because there is such a great number of possibilities. Therefore, helpful tutorials and example workflows, which are free of charge, are available to help get started. In addition, a detailed description for every node can be found in KNIME-Hub.

Basically, a workflow starts with data input, contains different nodes for filtering/visualization/analyzation in the middle and ends with one or more outputs.

My Workflow

The greatest advantage in my case was that KNIME has a specific node for the interaction with ChEMBL. On this account, I could get all the information for starting my thesis with one node.

In my workflow I was using 12 different nodes, whereas some of them were used more than once. In particular, the “Row Splitter”-, “Rule Based Row Splitter”- and the “GroupBy”-node were extremely helpful for filtering options. The “Excel Reader” and “Excel Writer” were used for in- or output of data.

Clustering nodes with different annotations helped me to maintain the overview.

In Figure 1, the yellow part contains data input, the search in ChEMBL with UniProt Accession-number, and the connection of these. The violet part contains the node “Table creator” where I defined the ring size from r10 to r40. In the green part, data I collected was combined with the defined ring size. Because I focused on small molecules, non-matching molecules to previous defined ring sizes, are representing my first output. This means, every molecule with a smaller ring size than 10 was used for the following analysis. With the “Duplicate-Row Filter” it was possible to look at unique molecules closer. The blue part is standing for all the molecules with a pChEMBL-value and further analysis. In the orange part median molecular properties were calculated.

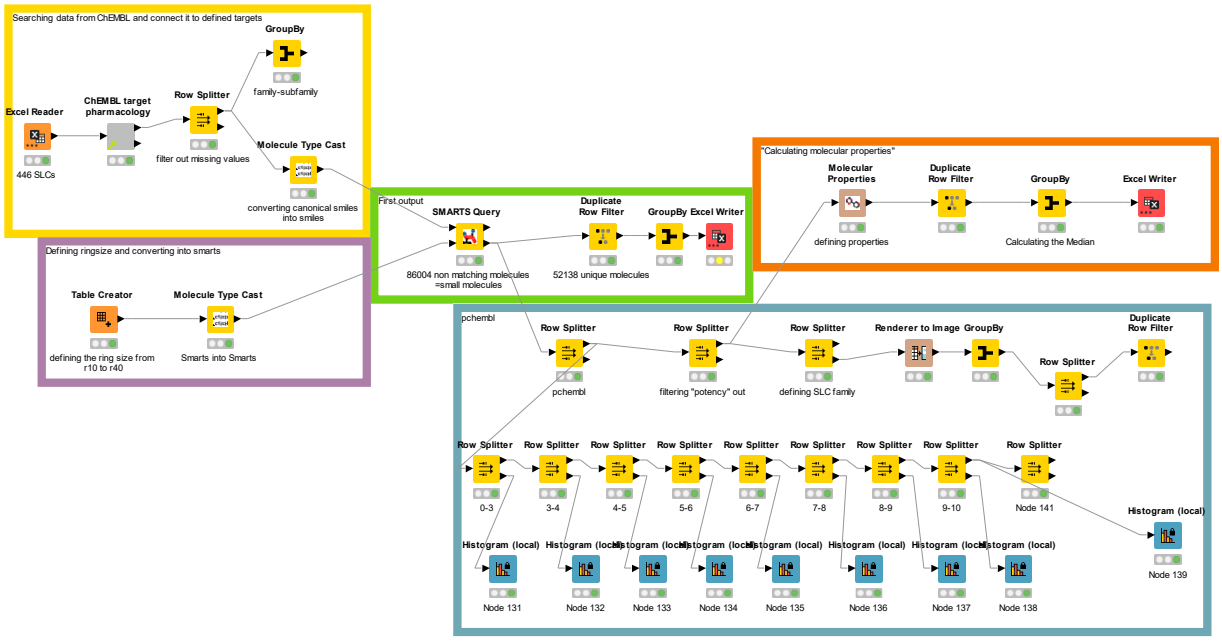


Figure 1: Screenshot of my workflow in KNIME

Results

Searching data out of ChEMBL and connecting it to defined targets

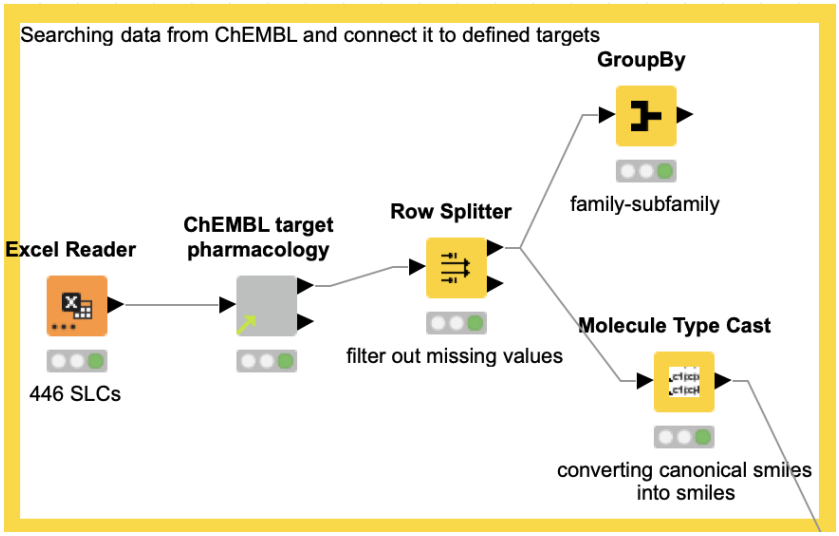


Figure 2: Extract of first steps in KNIME- workflow

With using the node "ChEMBL target pharmacology", not only information about which molecules bind to the defined SLCs has been received, but also molecular properties and data comments, which gave the opportunity for further analysis. Basically, all existing information in ChEMBL for every molecule binding to defined Solute carriers was gained with this one node.
With ChEMBL version 28, I received 86.725 hits of interaction with 120 SLC transporter out of the previous defined 446 targets. This means that for 325 SLC transporter no hits were achieved. Only 37 percent of initially defined transporter are representing targets for molecules. When we talk about SLC families, for 38 out of 65, interaction measurements are existing in ChEMBL. 27 SLC families do not provide any hits.

Defining ring size and converting into smarts

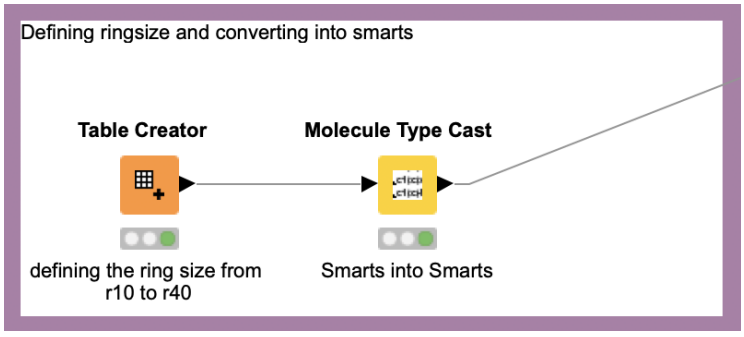


Figure 3: Extract of second step in KNIME-workflow

The second step to minimize data, obtained from ChEMBL, was focusing on drug-like molecules. While in my research group macromolecules where already processed (Diploma thesis Nejra Granulo), which were defined as all molecules with a ring size bigger than 10, my focus was on small molecules. Small molecules, which also can be named as drug-like molecules, were defined as all structures with a smaller ring size than 10. Therefore, the node “Table Creator” was used. Molecules with ring size between 10 and 40 were defined and afterwards filtered out. As expected, this filtering option did not really change the amount of data. Only 721 macromolecules were filtered out.

First output

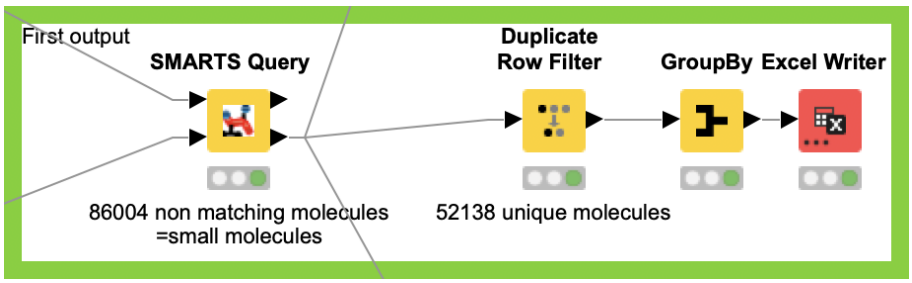


Figure 4: Extract of first output-nodes in KNIME-workflow

Looking at an output of 86.004 small molecules was the first possibility to recognize tendency. For 38 SLC families and 120 SLC subfamilies, interaction measures are existing in ChEMBL. This means, that with the filtering option for small molecules, targets stay the same as with before included macromolecules.
As mentioned, former research was focused on specific SLCs, for which reason the amount of existing data differs from transporter to transporter. In the following histogram the quantity of binding measurements for different SLC families can be identified.

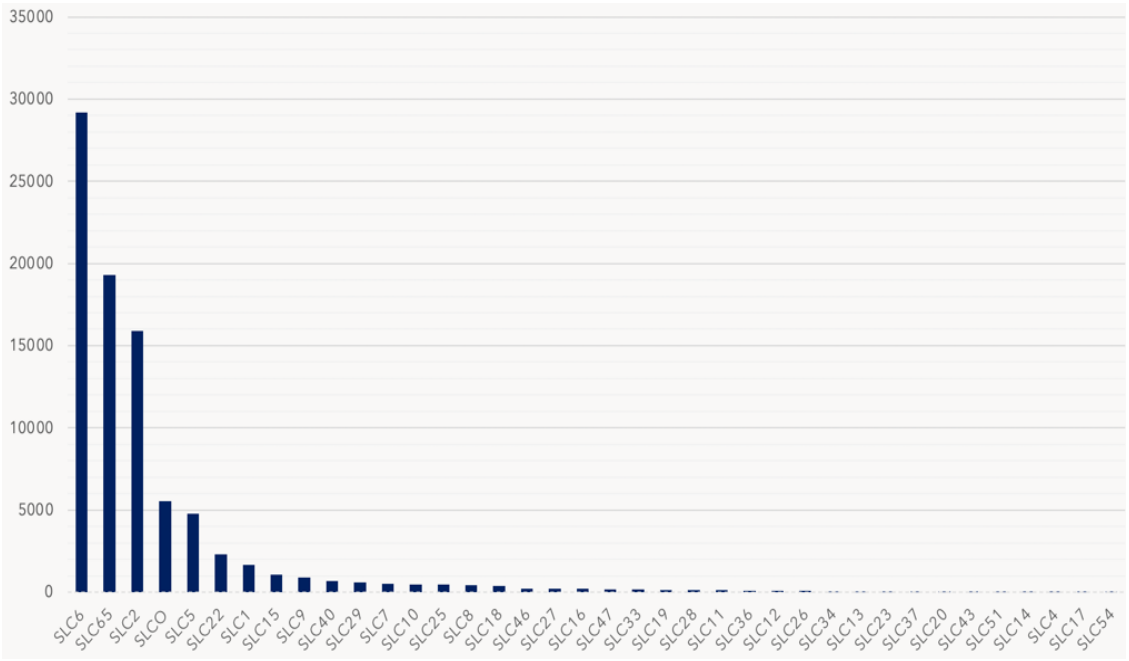


Figure 5: Histogram of data distribution between SLC families

In the histogram, SLC6, SLC65, and SLC2 can be recognized as favorable targets. While this leads to the proposal that these Solute carrier families are the most important ones when it comes to drug discovery, the following table of all 38 SLC families, with precise numbers of hits, should also point out often forgotten Solute carrier families. “Total Hits” are ranked from highest to lowest number of available data in ChEMBL. This changes when looking at “Unique molecules”. The percentage of unique molecules within the total number of hits can be seen on the right. The importance of considering “Duplicates” will be discussed later.

Table 1: Table of SLC families for which data is available in ChEMBL

SLC Family	Total Hits	Unique molecules	%
SLC6	29.175	9.616	33%
SLC65	19.291	18.916	98%
SLC2	15.907	13.994	88%
SLCO	5.521	2.146	39%
SLC5	4.786	3.130	65%
SLC22	2.295	1.038	45%
SLC1	1.669	345	21%
SLC15	1.064	395	37%
SLC9	901	589	65%
SLC40	691	454	66%
SLC29	596	336	56%
SLC7	510	207	41%
SLC10	483	359	74%
SLC25	480	243	51%
SLC8	424	390	92%
SLC18	380	274	72%
SLC46	228	52	23%
SLC27	214	129	60%
SLC16	194	130	67%
SLC47	190	70	37%
SLC33	151	144	95%
SLC19	128	61	48%
SLC28	123	82	67%
SLC11	108	96	89%
SLC36	100	50	50%
SLC12	98	29	30%
SLC26	89	45	51%
SLC34	62	19	31%
SLC13	45	13	29%
SLC23	28	6	21%
SLC37	25	23	92%
SLC20	24	12	50%
SLC43	7	7	100%
SLC51	6	4	67%
SLC14	4	3	75%
SLC4	3	3	100%
SLC17	2	1	50%
SLC54	2	2	100%

Duplicates

For some molecules more than one binding result is present in ChEMBL. Filtering for only unique molecules with the node “Duplicate Row Filter”, the number of 86.004 total hits was minimized to 52.138. Doing this for each family separately, big differences can be recognized.

For the SLC6 family, which is also called “Sodium and chloride dependent neurotransmitter transporter family”, lots of research has been performed. 29.175 total hits were received for this family. When looking at how much unique molecules bind to this family, only 9.616 are left, while 19.559 duplicates were found. This means that the amount of different molecules is approximately only one-third of the available data for SLC6 family. An explanation for this amount on duplicates can be, that the knowledge of related diseases with targets like the SLC6 family, triggers interest for many scientists to discover new drugs interacting with transporters belonging to this family. This leads to many different measurement-values for the same target, with the same potential drugs. Examples for molecules with most frequent binding measurements are Fluoxetine, Cocaine, and Gamma-Aminobutyric Acid.

As in the following screenshot demonstrated, 61 different values are existing for the interaction between SLC6A4 and Fluoxetine. Cocaine is often used for comparative study, that is why there are 58 binding results with SLC6A4 and 52 binding results with SLC6A2.

SLC6A12 mediates the rapid removal of GABA and maintains low extracellular levels. On this account it is not surprising that there are a lot of results for interaction with Gamma-Aminobutyric Acid.

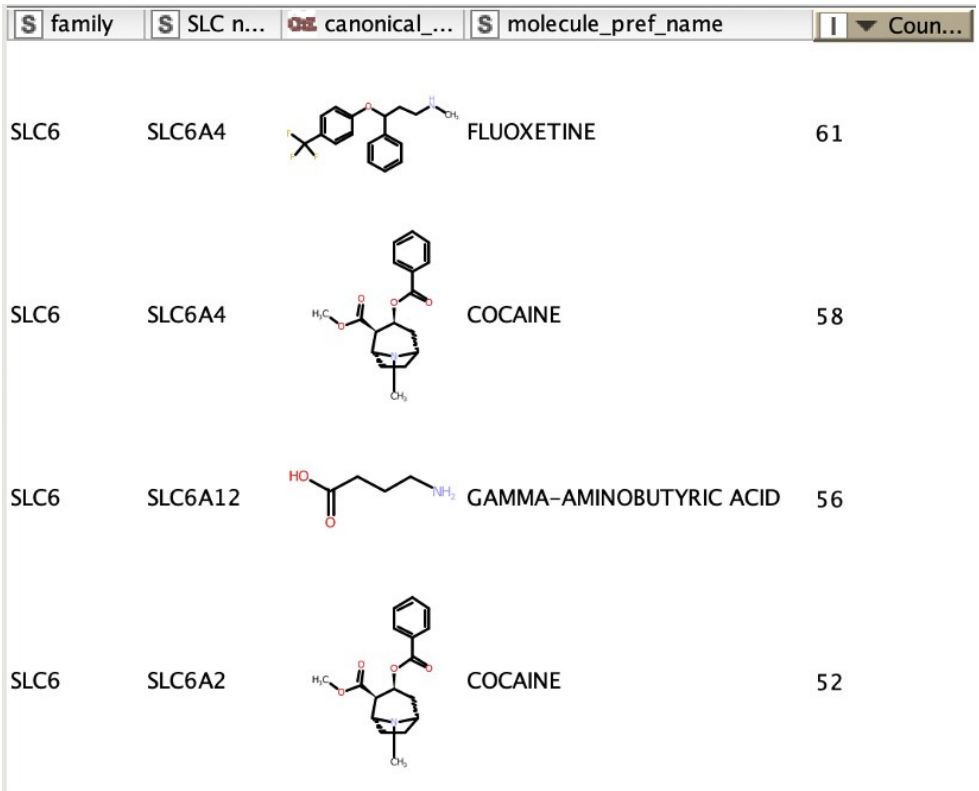


Figure 6: Screenshot of the molecules that interact most frequently with SLC6 transporters

SLC65 represents the family with the second highest number of hits. 19.291 measurements with small molecules are available in the ChEMBL-Database. In contrast to the SLC6 family, only 375 duplicates are amongst this table of hits. This means, that after filtering for only unique molecules, SLC65 is with 18.916 counts the family with the highest number of hits. Solute carriers for which the percentage on duplicates is notably high, are, apart from SLC6, SLC1, SLC15, SLCO, SLC22 and SLC46. To give some examples:
For SLC1 the two structures which can be identified in the screenshot, are molecules with the highest number of measurements.

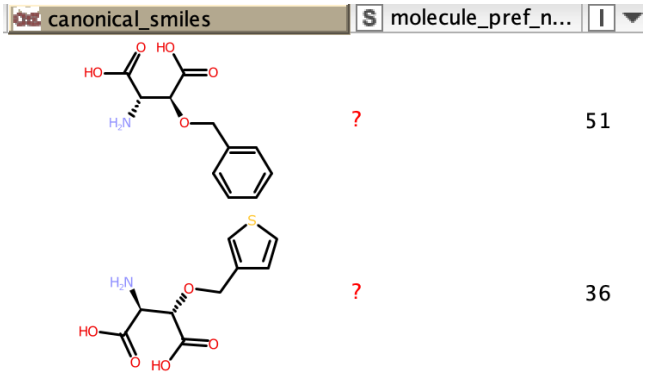


Figure 7: Molecules that interact the most frequently with SLC1 transporters

For SLC22, Probenecid and Cimetidine are the most frequent binding molecules. Glycylsarcosine and Valacyclovir are very often measured molecules with SLC15 as target.
For SLCO Estrone Sulfuric Acid (with 78 values) and Estradiol-17B Glucuronide (with 38 values) are the most frequent binding molecules.
29 different values were measured for the interaction between SLC46 and Pemetrexed.

The other way round, what also should be kept in mind is, that molecules can of course bind to more than one SLC transporter. This means there are counts for duplicates because binding measurements are available for different targets. In the following screenshot molecules which bind the highest number of different SLC transporter are shown. Methotrexate (an immune-system suppressant) is interacting with 17 different targets, whereby for some of them more than one activity value is present in ChEMBL. This also applies to other drugs, like Cimetidine (a Histamine H2 receptor antagonist), Benzylpenicillin (antibiotic), Furosemide (loop diuretic), Dinoprostone (Prostaglandin), and many more.

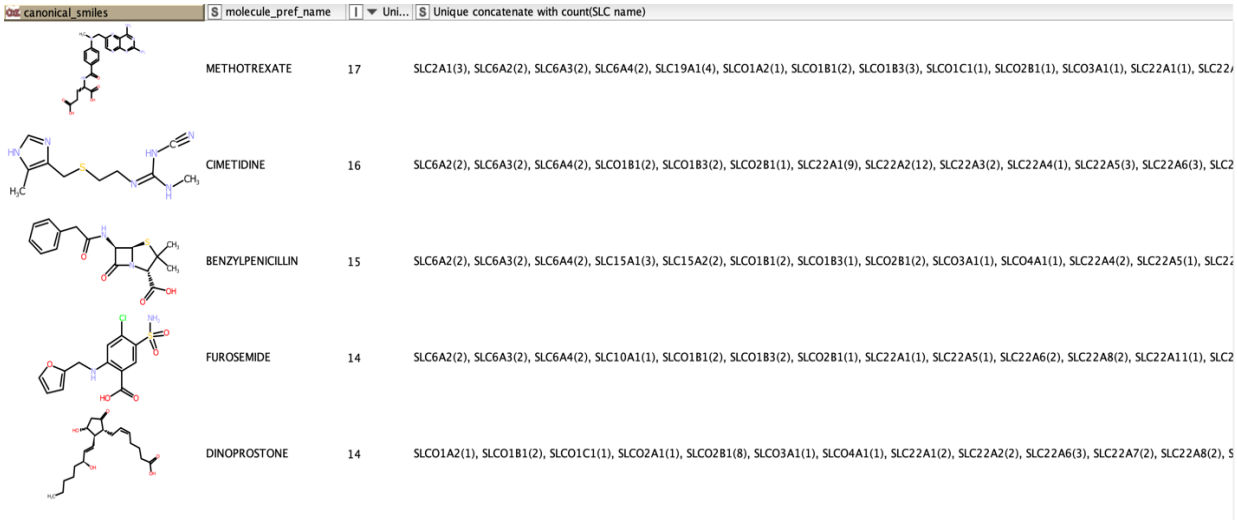


Figure 8: Molecules that interact with the highest number of different targets

Visualization of obtained data

To get a first overview of existing data, a sunburst diagram was used. The inner circle represents the type of data (inhibition/only binding/no available data). The middle circle names SLC families, and the outer circle represents related SLC transporter (also named as SLC subfamilies).

As already mentioned, SLC6 and SLC22 are pioneers in scientific investigations, that is why the range of identified subfamilies is much larger in these families than in others.

SLC2, SLC1 and SLC5 are also representing a great part in the world of solute carriers. SLC65 is an exception because it only contains two subfamilies-SLC65A1 and SLC65A2, nevertheless, lot of research has been investigated as the number of hits demonstrates.

What is interesting to see in the sunburst diagram is that there is still a big part where no data was found in ChEMBL. Even though the existence of some SLCs is known, no measurements with molecules were made or documented.

To sum this up, 38 SLC families have delivered results. Three of them are families which only show binding affinity with small molecules but do not get inhibited by any of them. For 27 SLC families, no data is available yet.

In the sunburst diagram, it was of interest to also point out the amount on non-existing data. As for 27 families this worked fine and a good overview is provided, it was not possible to visualize 311 subfamilies for which no data is available in ChEMBL. For this reason, a list of all SLC subfamilies with no existent data is provided below.

SLC1A6	SLC17A3	SLC23A1	SLC25A33	SLC26A8	SLC35D1	SLC38A3	SLC41A2	SLC51B	SLC6A8
SLC1A7	SLC17A4	SLC23A3	SLC25A34	SLC27A3	SLC35D2	SLC38A4	SLC41A3	SLC52A1	SLC60A1
SLC10A3	SLC17A5	SLC24A1	SLC25A35	SLC27A6	SLC35D3	SLC38A5	SLC42A1	SLC52A2	SLC61A1
SLC10A4	SLC17A6	SLC24A2	SLC25A36	SLC29A3	SLC35D4	SLC38A6	SLC42A2	SLC52A3	SLC62A1
SLC10A5	SLC17A7	SLC24A3	SLC25A37	SLC3A1	SLC35E1	SLC38A7	SLC42A3	SLC53A1	SLC63A1
SLC10A6	SLC17A8	SLC24A4	SLC25A38	SLC3A2	SLC35E2	SLC38A8	SLC43A2	SLC54A1	SLC63A2
SLC10A7	SLC17A9	SLC24A5	SLC25A39	SLC30A1	SLC35E2B	SLC38A9	SLC43A3	SLC54A3	SLC63A3
SLC12A1	SLC18B1	SLC25A1	SLC25A4	SLC30A10	SLC35E3	SLC39A1	SLC44A1	SLC55A1	SLC64A1
SLC12A3	SLC19A3	SLC25A10	SLC25A40	SLC30A2	SLC35E4	SLC39A10	SLC44A2	SLC55A2	SLC7A1
SLC12A4	SLC2A10	SLC25A11	SLC25A41	SLC30A3	SLC35F1	SLC39A11	SLC44A3	SLC55A3	SLC7A10
SLC12A5	SLC2A11	SLC25A12	SLC25A42	SLC30A4	SLC35F2	SLC39A12	SLC44A4	SLC56A1	SLC7A13
SLC12A6	SLC2A12	SLC25A13	SLC25A43	SLC30A5	SLC35F3	SLC39A13	SLC44A5	SLC56A2	SLC7A14
SLC12A7	SLC2A13	SLC25A14	SLC25A44	SLC30A6	SLC35F4	SLC39A14	SLC45A1	SLC56A3	SLC7A2
SLC12A8	SLC2A6	SLC25A15	SLC25A45	SLC30A7	SLC35F5	SLC39A2	SLC45A2	SLC56A4	SLC7A3
SLC12A9	SLC2A7	SLC25A16	SLC25A46	SLC30A8	SLC35F6	SLC39A3	SLC45A3	SLC56A5	SLC7A4
SLC13A1	SLC22A10	SLC25A17	SLC25A47	SLC30A9	SLC35G1	SLC39A4	SLC45A4	SLC57A1	SLC7A6
SLC13A4	SLC22A13	SLC25A18	SLC25A48	SLC31A1	SLC35G2	SLC39A5	SLC46A2	SLC57A2	SLC7A7
SLC14A2	SLC22A14	SLC25A19	SLC25A49	SLC31A2	SLC35G3	SLC39A6	SLC46A3	SLC57A3	SLC7A9
SLC15A3	SLC22A15	SLC25A2	SLC25A51	SLC32A1	SLC35G4	SLC39A7	SLC48A1	SLC57A4	SLC8A2
SLC15A4	SLC22A17	SLC25A21	SLC25A52	SLC33A2	SLC35G5	SLC39A8	SLC49A1	SLC57A5	SLC8A3
SLC15A5	SLC22A18	SLC25A22	SLC25A53	SLC35A1	SLC35G6	SLC39A9	SLC49A2	SLC57A6	SLC9A4
SLC16A10	SLC22A23	SLC25A23	SLC25A7	SLC35A2	SLC36A2	SLC4A1	SLC49A3	SLC58A1	SLC9A6
SLC16A11	SLC22A24	SLC25A24	SLC25A8	SLC35A3	SLC36A3	SLC4A10	SLC49A4	SLC58A2	SLC9A7
SLC16A12	SLC22A25	SLC25A25	SLC25A9	SLC35A4	SLC36A4	SLC4A11	SLC5A10	SLC59A1	SLC9A8
SLC16A13	SLC22A31	SLC25A26	SLC26A1	SLC35A5	SLC37A1	SLC4A2	SLC5A12	SLC59A2	SLC9A9
SLC16A14	SLC22A32	SLC25A27	SLC26A10	SLC35B1	SLC37A2	SLC4A3	SLC5A3	SLC6A14	SLC9B1
SLC16A2	SLC22B1	SLC25A28	SLC26A11	SLC35B2	SLC37A3	SLC4A4	SLC5A5	SLC6A16	SLC9B2
SLC16A4	SLC22B2	SLC25A29	SLC26A2	SLC35B3	SLC38A1	SLC4A5	SLC5A6	SLC6A17	SLC9C1
SLC16A5	SLC22B3	SLC25A30	SLC26A5	SLC35B4	SLC38A10	SLC4A8	SLC5A8	SLC6A18	SLC9C2
SLC16A6	SLC22B4	SLC25A31	SLC26A6	SLC35C1	SLC38A11	SLC4A9	SLC5A9	SLC6A19	SLCO1B7
SLC16A9	SLC22B5	SLC25A32	SLC26A7	SLC35C2	SLC38A2	SLC41A1	SLC50A1	SLC6A20	SLCO5A1
									SLCO6A1

Figure 9: List of all SLC transporter with no existent data in ChEMBL

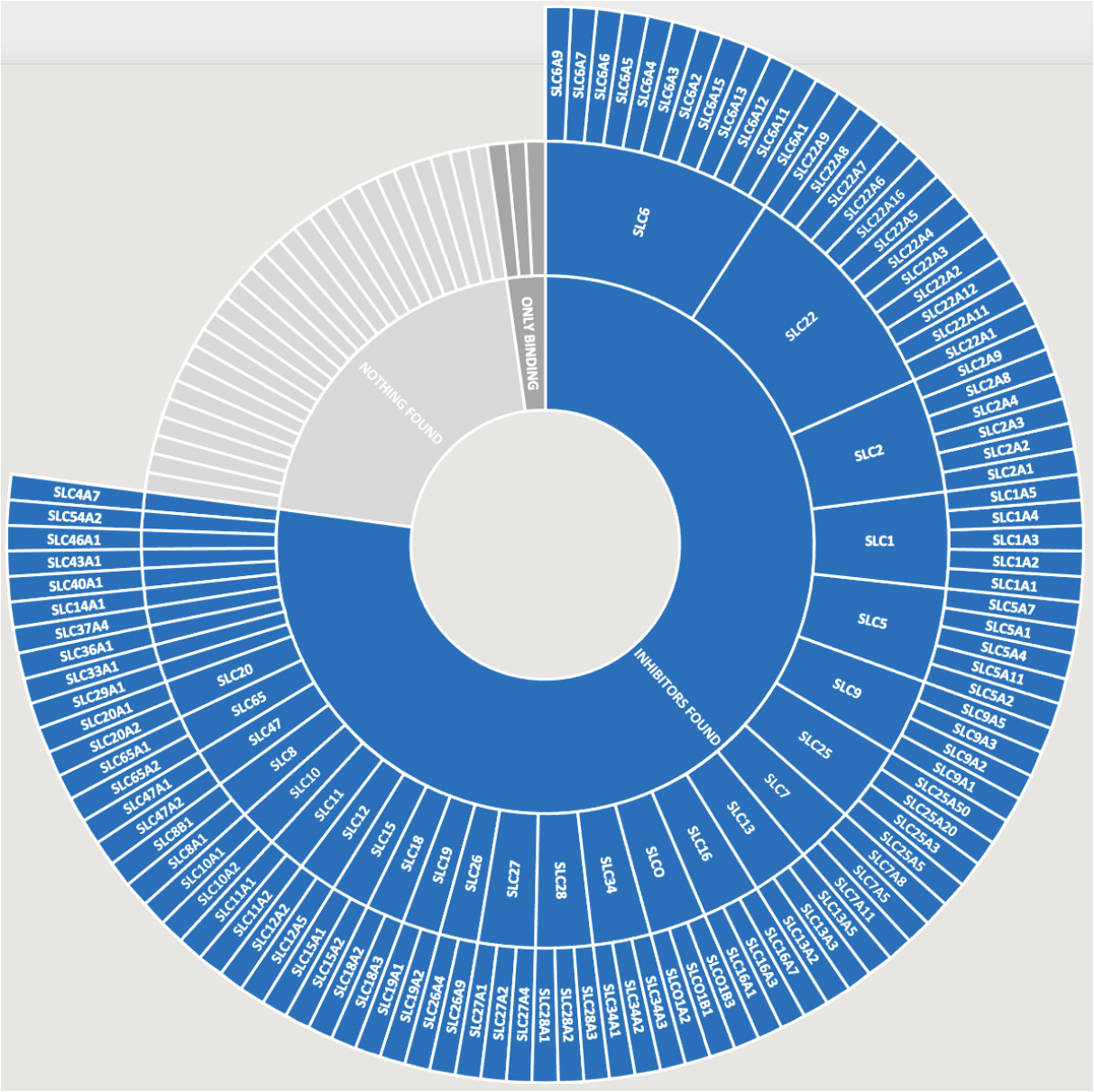


Figure 10: Sunburst image of SLC families and their subfamilies

Listing 27 SLC families, where no molecule binding interaction is present in ChEMBL, with their full name, is intended to provide overview.

Solute carrier families with no available data:
SLC3: amino acid transporter family: subfamilies
SLC24: Na+/(Ca2+-K+) exchanger family
SLC30: Zinc efflux family
SLC31: Copper transporter family
SLC32: Vesicular inhibitory amino acid transporter family
SLC35: Nucleoside-sugar transporter family
SLC38: System A and System N sodium-coupled neutral amino acid transporter family
SLC39: Metal ion transporter family
SLC41: MgtE-like magnesium transporter family
SLC42: Rh ammonium transporter family
SLC44: Choline-like transporter family
SLC45: H+/sugar cotransporter family
SLC48: Heme transporter family
SLC49: FLVCR-related transporter family
SLC50. Sugar efflux transporters
SLC52: Riboflavin transporter family
SLC53: Phosphate carriers
SLC55: Mitochondrial cation/proton exchangers
SLC56: Sideroflexins
SLC57: NiPA-like magnesium transporter family
SLC58: MagT-like magnesium transporter family
SLC59: Sodium-dependent lysophosphatidylcholine symporter family
SLC60: Glucose transporters
SLC61: Molybdate transporter family
SLC62: Pyrophosphate transporters
SLC63: Sphingosine-phosphate transporters
SLC64: Golgi Ca2+/H+ exchangers

Another differentiating factor was the type of binding. There are three SLC transporter, for which some interaction with molecules was measured, but which do not get inhibited.

SLC families which show binding without further characterisation:
SLC17: Vesicular glutamate transporter family
SLC23: Na+-dependent ascorbic acid transporter family
SLC51: Transporters of steroid-derived molecules
http://slc.bioparadigms.org

As already said, 65 families are known by now. 27 SLC families do not provide any hits and three only show binding to compounds without further specification. This means that some interaction potency for molecules with these three targets was measured and documented in ChEMBL, but no molecule shows inhibition potential. For the remaining 35 SLC families inhibitors are present in ChEMBL. As the focus in my thesis was on this type of compounds, I will discuss them in more detail. As the simple knowledge of inhibition potential does not suffice for accurate analysis, the pChEMBL value was decisive in this thesis.

pChEMBL-value

There are multiple values that describe inhibition. In CheMBL these values are named as: pIC50, IC50, pKi, Ki, Inhibition, EC50, and even more. To receive accurate results, it was important to focus on one specific value. The most precise evidence is given by the so called "pchembl value". pChEMBL is demonstrating measures of half-maximal response/affinity/potency on a negative logarithmic scale. The pChEMBL value is currently defined as follows: $-\log_{10}$ (molar IC50, XC50, EC50, AC50, Ki, Kd or Potency). (10)

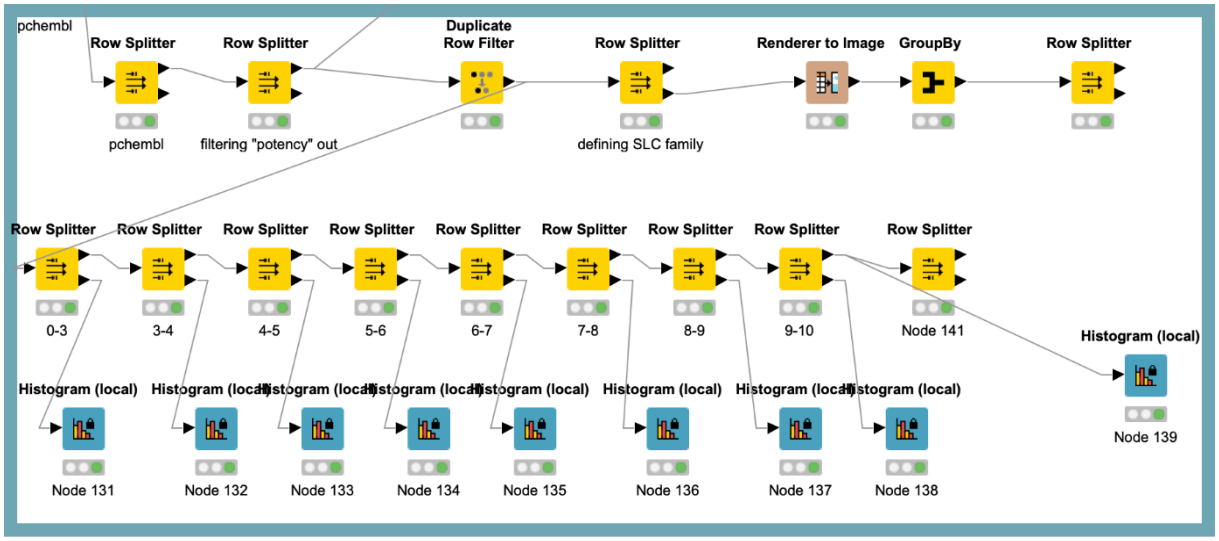


Figure 11: Extract of pchembl-nodes in KNIME-workflow

To focus on only inhibiting drug-like molecules, the node Row-Splitter was required. First, all molecules with no present pchembl value were filtered out. 43878 molecules with available pchembl-values were left. After that, all molecules which had the binding description "potency" were filtered out, to focus only on inhibiting data. Remained standard values (which means interaction values) were IC50, EC50, Kd and Ki.
25304 inhibitors were received after all this filtering options, which interact with 33 SLC families and 88 subfamilies. SLC 36 and SLC4 were excluded as targets-families and SLC1A4, SLC2A9, SLC6A6, SLC7A8, SLC11A2, SLC16A7, SLC22A4, SLC22A5, SLC22A7, SLC22A9, SLC25A3, SLC25A50, SLC26A9 and SLCO1A2 were excluded as target-subfamilies for "inhibitors with pchembl-values existent".

Duplicates

After running the acquired data through a “Duplicate Row Filter”-node, 13131 unique molecules were left. These 13131 molecules are inhibiting 33 different SLC families/88 SLC subfamilies.

As already mentioned, there are molecules where interaction measurements were repeated, because their results are of particular interest. As there are, like before, Fluoxetine, Cocaine and Gamma-Amino-Butyric Acid most frequent inhibitors for SLC6 family, Dapagliflozin is with 61 different measurements one of the mainly studied inhibitors for SLC5 family members.

SLC1, with only 27% unique molecules, and SLCO, with 32% unique molecules, belong to targets where most duplicates are present.

While for Estrone Sulfuric Acid and Estradiol-17B Glucuronide most binding values were available in ChEMBL, Ritonavir, Silibinin and Erlotinib show after filtering options the highest number of inhibiting measurements for the SLCO family. Estrone Sulfuric Acid and Estradiol-17B Glucuronide are only binding to SLCO, but do not have inhibiting potential.

Examples like this can be found for nearly every SLC-family. The highest number of molecules which got “lost” after filtering for only inhibitors with a pchembl-value available, can be found for SLC2 and SLC65. It is interesting to see how SLC65 changed its position of ranking. 18778 molecules available for that family are only binding or do not have a pchembl-value existent. In the opposite, SLC40, SLC33 and SLC54 are exclusive targets for inhibitors.

SLC26 and SLC46 are also targets with a low percentage of unique inhibitors. SLC46, for example, counts 12 hits for inhibition measurements with Pemetrexed.

When searching for molecules which interact with more than one target, Mitoxantrone (antineoplastic agent), Ritonavir (antiretroviral medication), Imipramine (tricyclic antidepressant), Bithionol (antibacterial and anthelmintic drug), Pentamidine (antimicrobial medication) and Ethinyl Estradiol (estrogen drug) are inhibiting the highest number of different SLC transporter.

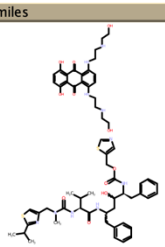
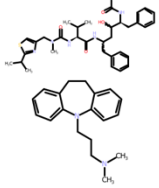
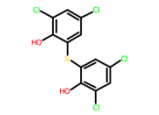
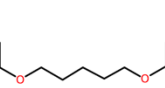
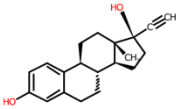
canonical_smiles	molecule_pref_na...	Uni...	Unique concatenate with count(SLC name)
	MITOXANTRONE	7	SLC6A2(2), SLCO1B3(2), SLC22A1(1), SLC22A2(1), SLC22A3(1), SLC47A1(3), SLC47A2(2)
	RITONAVIR	7	SLCO1B1(5), SLCO1B3(2), SLCO2B1(2), SLC22A1(1), SLC22A2(1), SLC47A1(3), SLC47A2(2)
	IMIPRAMINE	7	SLC6A2(2), SLC6A3(1), SLC6A4(29), SLC22A1(3), SLC22A2(1), SLC22A3(1), SLC47A1(1)
	BITHIONOL	7	SLC6A2(2), SLC6A3(2), SLC22A1(2), SLC22A2(1), SLC22A3(1), SLC47A1(1), SLC47A2(1)
	PENTAMIDINE	7	SLC6A2(2), SLC6A3(2), SLC22A1(1), SLC22A2(1), SLC22A3(1), SLC47A1(3), SLC47A2(2)
	ETHINYL ESTRADIOL	6	SLC6A2(2), SLC6A3(2), SLC6A4(2), SLC22A2(1), SLC47A1(1), SLC47A2(1)

Figure 12: Inhibitors with pchembl-values available that interact with the highest number of different targets

Visualization of obtained data

Filtering only for molecules with an existing pchembl value provided an overview of which SLC families and SLC targets get inhibited more likely than others. Knowing that SLC6 is present as target for more than 6000 unique inhibitors makes us understand that it takes a leading role in therapy of various diseases. But also the fact that for some SLC transporter only two unique inhibitors are available in ChEMBL is no sign that this Solute carrier cannot play an important role in drug discovery.

To visualize the amount on inhibitors with a pchembl-value existing, the sunburst image from above was used and colored. Different colors represent different counts on the total number of hits. Grey colored SLC families, which in the previous sunburst image were colored blue, show that they were filtered out because no pchembl-value is existing. Blue stands now for all targets for which less than 100 molecules with pchembl-values were found. Yellow colored fields are representing SLCs with over 100 counts, orange stands for over 300 counts, green means more than 500 counts, violet is representing over 2000 counts and red color represents targets for which over 10000 pchembl values are available in ChEMBL version 28.

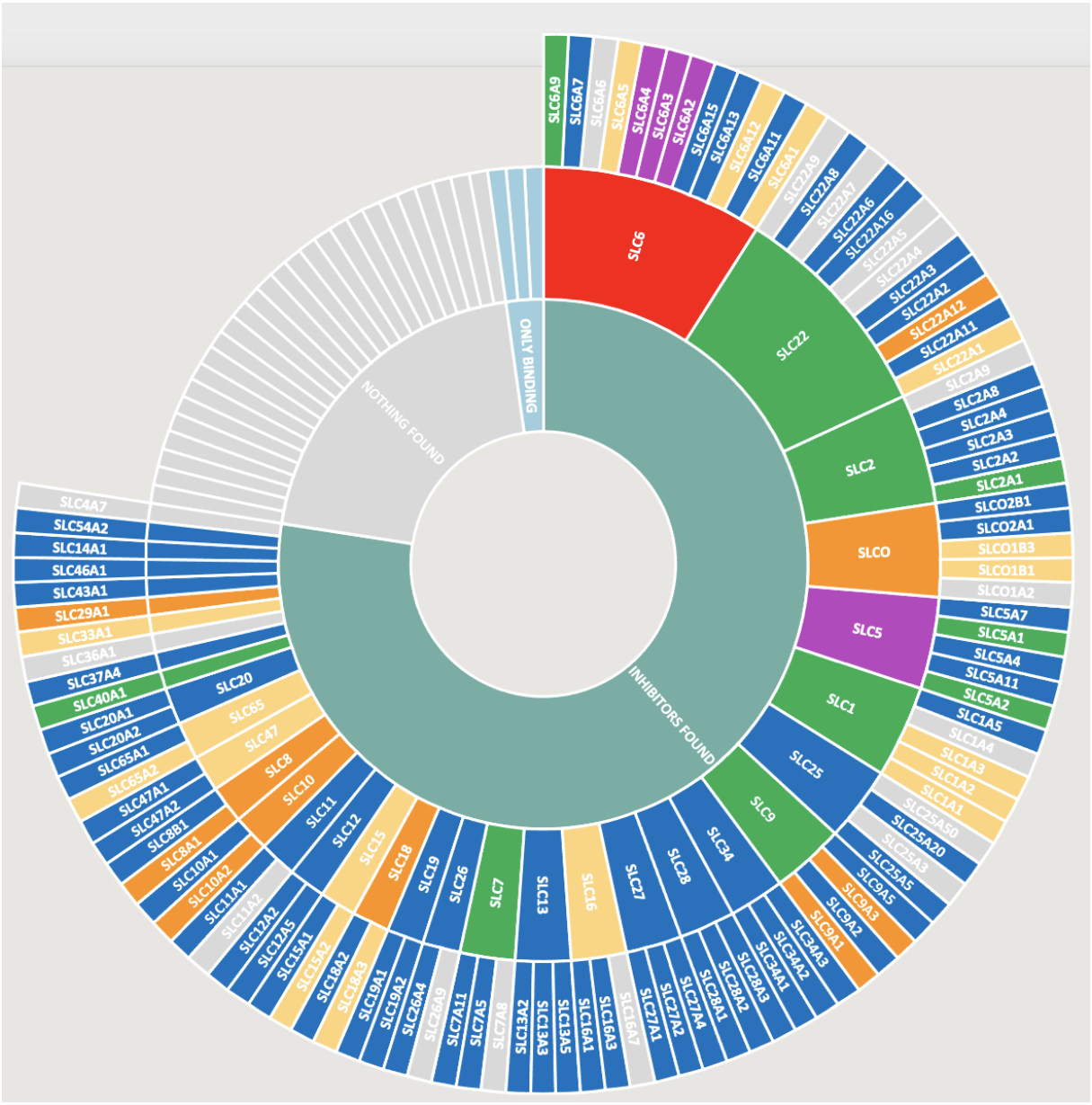


Figure 13: Sunburst image colored after the number of inhibitors with pchembl-values available in ChEMBL

What immediately can be recognized is, that there are 2 families and 14 subfamilies which are colored grey. This means, molecules which were found for these targets do not have a pchembl value existent in ChEMBL, or only some "potency" was measured.
For 33 SLC families (88 SLC subfamilies) pchembl-values are available, and their standard value is either IC50/EC50/Kd or Ki.
To look at each family more precisely, the node "Row Splitter" was useful again. For every family, the settings were changed. With the node "Rendered to Image" it was possible to take a look at each structure which is inhibiting the previously defined SLC family. To get an insight in how transporter and their inhibiting molecules differ from each other, a short summary of every inhibited SLC family and screenshots of inhibiting structures with the highest pchembl-value should help understand why these targets are already - or can be of interest in future. This detailed list can be found in the "Discussion" section.
To get a correlation between the output of inhibitors with the previous output of total interaction measurements, the same table was used and updated with filtered output.

To demonstrate the number of molecules which got lost while filtering for only inhibitors, the fifth column was made. This means that the number of molecules in the last column shows the amount of "only binding" measurements or data with no pchembl-value existent. Coloring the columns of "total hits" with the same colors as in the related sunburst diagram should give a better overview of precise numbers of total counts. Outstanding numbers of "lost" molecules are highlighted in yellow.

Table 2: Table of SLC families for which data of inhibitiors with pchembl-values are available in ChEMBL

SLC Family	Total Hits	Unique inhibitors	%	Difference between "Unique molecules" and "Unique inhibitors with pchembl-value"
SLC6	15677	6746	43%	2870
SLC5	2889	1963	68%	1162
SLC2	843	712	84%	13282
SLC9	799	532	67%	57
SLC22	762	568	75%	470
SLC40	686	454	66%	0
SLC1	660	179	27%	166
SLC8	391	361	92%	29
SLCO	387	124	32%	2022
SLC10	334	297	89%	62
SLC29	321	240	75%	96
SLC18	314	245	78%	29
SLC15	188	93	49%	302
SLC33	151	144	95%	0
SLC65	146	138	95%	18778
SLC16	102	77	75%	53
SLC47	100	47	47%	23
SLC46	94	34	36%	18
SLC12	88	44	50%	7
SLC27	73	72	99%	57
SLC7	65	50	77%	157
SLC28	59	46	78%	36
SLC19	41	27	66%	34
SLC11	39	39	100%	57
SLC13	30	10	33%	3
SLC34	24	11	46%	8
SLC37	19	18	95%	5
SLC26	9	2	22%	43
SLC25	5	5	100%	238
SLC20	3	2	67%	10
SLC14	2	2	100%	1
SLC54	2	2	100%	0
SLC43	1	1	100%	6
SLC36	0			50
SLC4	0			3

Division of pChEMBL-values

It was of interest to look at the pchembl value in more detail. As already mentioned, pchembl indicates measures of half-maximal response on a negative logarithmic scale. To make this value more understandable I translated it into nanomolar concentration.
Pchembl value can be interpreted as follows:

Pchembl 10 = 0.1nm
Pchembl 9 = 1nm
Pchembl 8 = 10nm
Pchembl 7 = 100nm
Pchembl 6 = 1 000nm
Pchembl 5 = 10 000nm
Pchembl 4 = 100 000nm
Pchembl 3 = 1 000 000nm
Pchembl 2 = 10 000 000nm

This means that the bigger the pchembl value, the higher the inhibiting potential.
Molecules that are already inhibiting SLCs with a concentration of 0.1nm are very strong inhibitors. Examples: Paroxetine and Sertraline inhibit SLC6A4 with a concentration of 0.07 nM; Benzovesamicol inhibits SLC18A3 with a concentration of 0.05 nM.

Examples of inhibitors with a pchembl value of 9: Duloxetine, Fluoxetine, Amitriptyline and Clomipramine inhibiting SLC6A4; Maralixibat inhibiting SLC10A2; Nitrobenzylmercaptopurine inhibiting SLC29A1; Dapagliflozin inhibiting SLC5A2

Examples of inhibitors with a pchembl value of 8: Sergliflozin, Dapagliflozin, Canagliflozin, Ertugliflozin, Sotagliflozin inhibiting SLC5A2; Dextroamphetamine, Nortriptyline inhibiting SLC6A2; Vanoxerine inhibiting SLC6A3; Escitalopram inhibiting SLC6A4; Tenapanor inhibiting SLC9A3; Dipyridamole inhibiting SLC29A1

Examples of inhibitors with a pchembl value of 7: Glutamic acid inhibiting SLC1A1; Sotagliflozin inhibiting SLC5A1, Phlorizin inhibiting SLC5A2; Methylphenidate, Chlorpromazine and Levomilnacipran inhibiting SLC6A2; Reboxetine inhibiting SLC6A3; Primaquine inhibiting SLC6A4

Splitting up the SLC families as inhibited targets into pchembl areas.

Table 3: Table of pChEMBL-areas with their preferred targets

pChEMBL area	**Number of inhibiting molecules**	**Preferred targets**
0-3	8	SLC15
3-4	150	SLC2 > SLC40 > SLC1 > SLC15
4-5	2230	SLC6 > SLC1 > SLC2 > SLC22 > SLC5
5-6	6076	SLC6 > SLC2 > SLC5 > SLC40 >SLC1 >SLC22
6-7	6524	SLC6 > SLC5
7-8	5951	SLC6 > SLC5
8-9	3639	SLC6 > SLC5 > SLC33 > SLC9
9-10	621	SLC6 > SLC5
>10	61	SLC6 > SLC16 > SLC18 > SLC29

Calculating the median molecular properties

To achieve a quick overview on a big number of structures, I had to select only a few characteristics which should describe molecules and their differences the best way possible. Aromatic Atoms Count, Rotatable Bonds Count, Topological Polar Surface Area and Molecular Weight were well-chosen molecular properties.

It is known that reduced molecular flexibility, which means a low number of rotatable bonds, and low topological polar surface area (TPSA), are found to be important predictors of good oral bioavailability, independent of molecular weight.

Compounds with 10 or fewer number of rotatable bonds and topological surface area equal to or less than 140 Angstrom, have a high probability of good intestinal permeability and fraction of dose which is absorbed in human. Moreover, it is indicated that a lower number of hydrogen bond counts and higher logD and logP values are associated with higher permeability and bioavailabilty of drugs. (11)

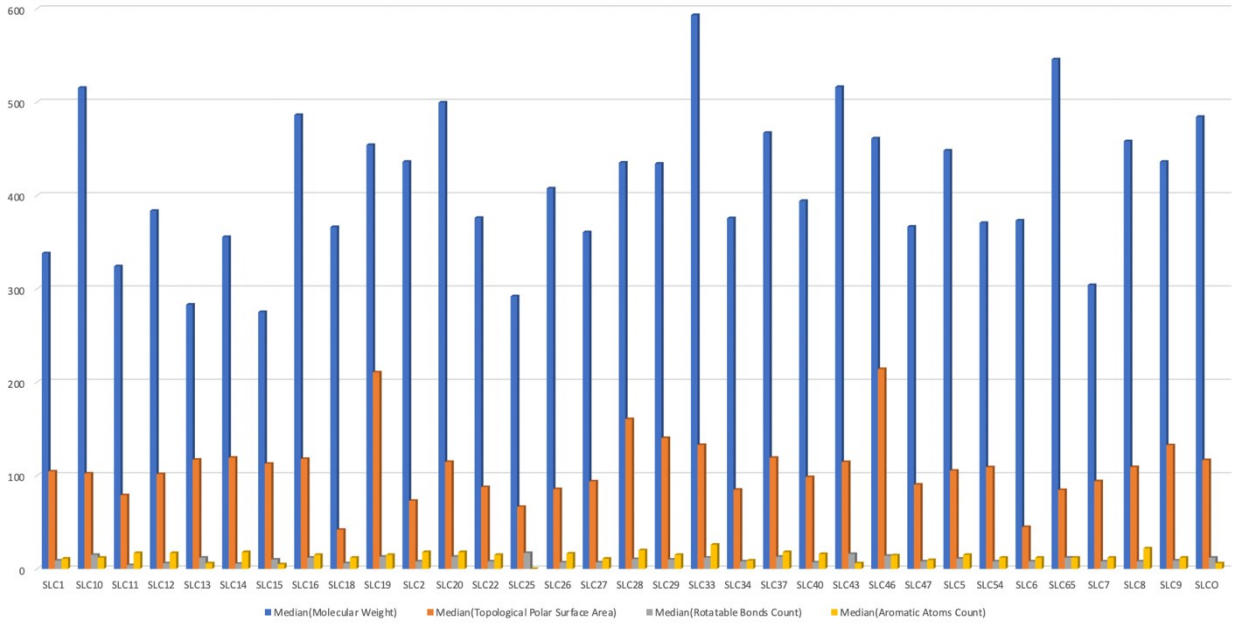


Figure 14: Visualization of median molecular properties for each SLC family

Outstanding high median molecular weight can be identified for inhibitors for SLC33 (593), SLC65 (545), SLC43 (516) and SLC10 (515).

Very low median molecular weight of inhibiting molecules occurs at SLC15 (275), SLC13 (283) and SLC25 (292).

Lowest median topological polar surface area exists at SLC18 (41.9) and SLC6 (44.8).

Lowest median rotatable bonds count can be identified at SLC11 (4) and SLC14 (5.

Inhibitors of SLC33 (26), SLC8 (22) and SLC28 (20) family show high count on aromatic atoms, while all inhibitors for SLC25 show zero aromatic atoms. What should be kept in mind is, that there are only five molecules inhibiting SLC25.

This also must be considered for SLC43, where only one inhibitor (with this very high molecular weight) is existent. As well as the low median rotatable bonds count for SLC14 comes from only two inhibitors. A list with all calculated properties for each family and their associated count of inhibitors can be found in the appendix.

Discussion

The amount of data without filtering options is too big to look at each molecule in detail. Filtering for only well documented data, which means data with a pchembl-value available in CheMBL, and in addition filtering for only inhibiting small molecules, clears the way for a more detailed look.
The sunburst diagram, colored to get a quick overview of how many total hits are existent in the ChEMBL-database, was introduced in “Results”. In this discussion I will go into more detail for every colored SLC family. Ranking them from red colored Solute carriers to blue colored should provide a short insight in the family itself, and their molecules inhibiting them.
The aim was to show potential relations between the function of a Solute carrier and the preferred molecular structure of molecules with inhibiting potential. To get a better understanding of these structures, screenshots which contain inhibitors with the highest pchembl-value are provided. I tried to demonstrate particularly structures with a “molecule-preferred-name” available, because it is easier to understand the correlation between the function of a SLC and an already known inhibitor. For some families there are no named inhibitors available, and a red question mark is provided from KNIME. The number of “no named molecules” increases for families with a falling number of hits. This once again confirmed that research for developing drugs in the past years focused on particular SLC transporter families. It can be said that transporter families which are colored blue need to be further explored. In my thesis I wanted to point out the knowledge and important achievement which was made using Solute carriers as drug targets, but also emphasize the remaining capacity for new findings.
Starting with the family for which the highest number of hits was achieved and working off all Solute carrier families until the lowest number of counts should not rank the families from very important to less important. It is also of high interest to show a family where only two inhibitors are available, because exactly there, space for research can be immense.

Red colored SLCs = over 10 000 counts

SLC6: Sodium- and chloride-dependent neurotransmitter transporter family
SLC6 transporters can be divided in 4 subgroups. Neurotransmitter transporters, amino acid transporters, osmolyte transporters, and creatine transporters. The SLC6 family is the most researched Solute carrier family.
SLC6A4 and SLC6A2 are main targets for inhibitors. What is interesting is that there is no pchembl value measured for SLC6A6. This transporter is also named Sodium-dependent taurine and beta-alanine transporter. Diseases associated with SLC6A6 are Hypotaurinemic Retinal Degeneration and Cardiomyopathy. (12) This shows that there is still enough space for research left.

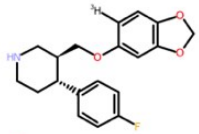
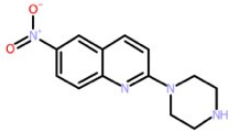
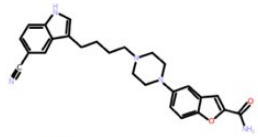
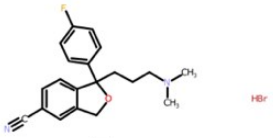
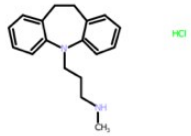
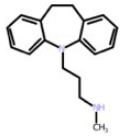
SLC n...	canonical_smiles	molecule_pref_name	pchembl_value
SLC6A4		[3H]PAROXETINE	10.1
SLC6A4		6-NITROQUIPAZINE	9.77
SLC6A4		VILAZODONE	9.3
SLC6A4		CITALOPRAM HYDROBROMI...	9.11
SLC6A2		DESIPRAMINE HYDROCHLO...	9.1
SLC6A2		DESIPRAMINE	9

Figure 15: Drug-like molecules inhibiting SLC6 transporter

Violet colored SLCs = over 2 000 counts

SLC5: Sodium glucose cotransporter family

SLC5A1 and SLC5A2, better known as SGLT1 and SGLT2, are associated with diseases like Glucose/ Galactose Malabsorption, Aminoaciduria and Renal Glucosuria. While SGLT1 is essential for fast absorption of glucose and galactose in the intestine, the expression of SGLT2 is highly restricted to the early part of the kidney proximal tubules, where it reabsorbs a major part of filtered glucose. SGLT2 has been successfully used by the pharmaceutical industry to develop effective new drugs for the therapy of diabetes mellitus. SGLT2 inhibitors work by preventing the kidneys from reabsorbing glucose back into the blood. (13) These inhibitors, called gliflozins, also show favorable nephroprotective and cardioprotective effects. Structures that should inhibit SLC5A2 preferential contain glucose residues in their molecular structure.

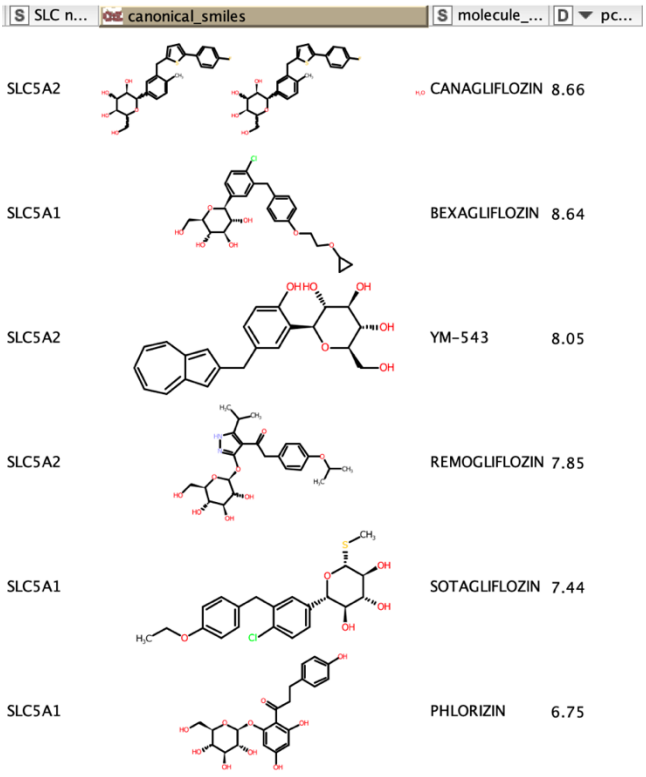


Figure 16: Drug-like molecules inhibiting SLC5 transporter

Green colored = over 500 counts

SLC1: High-affinity glutamate and neutral amino acid transporter family

Transporter of the SLC1 family play decisive roles in protecting neurons against glutamate excitotoxicity in the central nervous system. The regulation and manipulation of their function is a critical issue in the pathogenesis and treatment of CNS disorders involving glutamate excitotoxicity. Loss of function of the glial glutamate transporter GLT1 (SLC1A2) has been implicated in the pathogenesis of amyotrophic lateral sclerosis, resulting in damage of adjacent motor neurons. Selective inhibition of the neuronal glutamate transporter SLC1A1 may be of therapeutic interest, allowing blockage of glutamate exit from neurons due to "reversed glutamate transport" of SLC1A1, which will occur during pathological conditions such as during ischemia after a stroke. (14)

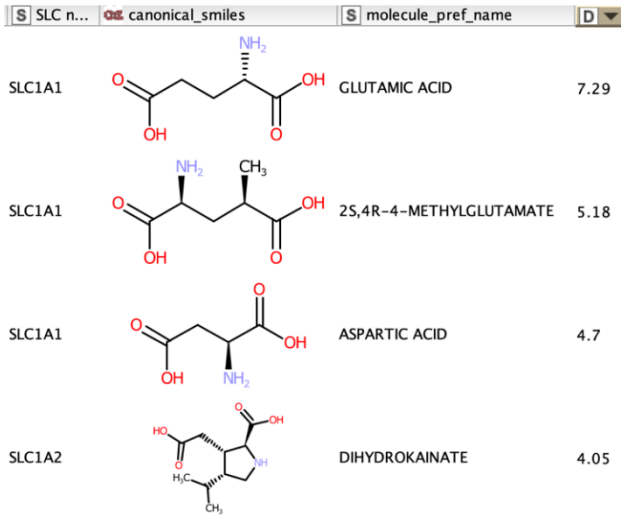


Figure 17: Drug-like molecules inhibiting SLC1 transporter

SLC2: Facilitative GLUT transporter family

All the GLUT proteins were originally presumed to catalyze hexose transport into and out of cells. Pathophysiological abnormalities in GLUT proteins are responsible for, or associated with, clinical problems including type 2 diabetes, cancer, and a range of tissue disorders related to tissue-specific GLUT protein profiles.

These glucose transporters are often rate limiting for subsequent metabolism and thus provide a point at which metabolic flux can be controlled. (15)

As it can be seen in the following screenshot, SLC2A1 is presently the leading target in the SLC2 family. The SLC2A1 gene encodes the glucose transporter type 1 (GLUT1) protein, which is responsible for transporting glucose across the blood–brain barrier. Recessive mutations of SLC2A1 can result in neuroglycopenia, which can cause dyskinesias and seizures. (16) Scientist also found that elevated SLC2A1 is a critical modulator in lung adenocarcinoma progression by modified glucose metabolism and the cell cycle pathway. That is why SLC2A1 is a promising target for lung adenocarcinoma therapy. (17) Even in breast cancer high expression of glucose transporter 1 suggests a key role in regulating cell metabolism. It is known that GLUT-1 inhibition shows anti-proliferation effects and that is why it is so important to prosecute investigation to better understand this target. (18)

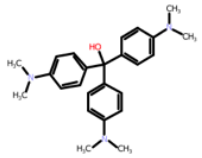
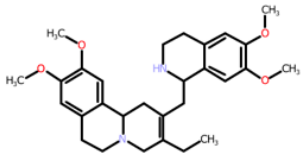
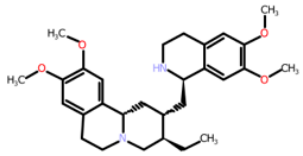
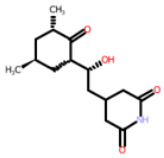
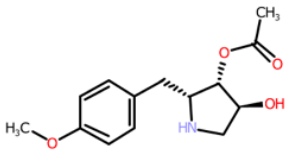
SLC n...	canonical_smiles	molecule_pref_na...	pc...
SLC2A1		METHYLROSANILINE	7.42
SLC2A1		DIHYDROEMETINE	7.2
SLC2A1		EMETINE	6.97
SLC2A1		CYCLOHEXIMIDE	6.64
SLC2A1		ANISOMYCIN	6.49

Figure 18: Drug-like molecules inhibiting SLC2 transporter

SLC9: Na+/H+ exchanger family

The SLC9 family plays a critical role in electroneutral exchange of Na^+ and H^+ in the mammalian intestine as well as other absorptive and secretory epithelia of digestive organs. These transport proteins contribute to the transepithelial Na^+ and water absorption, intracellular pH- and cellular volume regulation as well as the electrolyte, acid-base, and fluid volume homeostasis at systemic level. They also influence the function of other membrane transport mechanisms, affect cellular proliferation and apoptosis as well as cell migration, adherence to the extracellular matrix, and tissue repair. (19)

Altered SLC9 activity has been linked to the pathogenesis of several diseases, including essential hypertension, congenital secretory diarrhea, diabetes, and tissue damage caused by ischemia/reperfusion. (20)

Prominent inhibitors of SLC9 targets are Amiloride, Cariporide, Eniporide and Zoniporide.

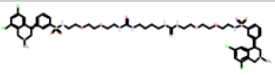
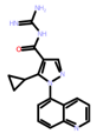
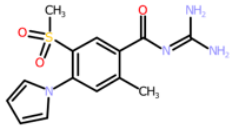
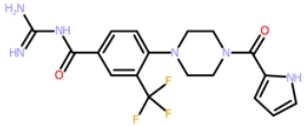
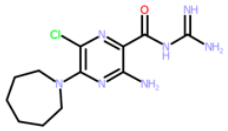
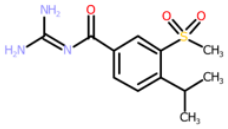
SLC n...	canonical_smiles	molecule_pref_name	p
SLC9A3		TENAPANOR HYDROCHLORIDE	8.2
SLC9A1		ZONIPORIDE	7.23
SLC9A1		ENIPORIDE	6.85
SLC9A1		SABIPORIDE	6.76
SLC9A5		N,N-HEXAMETHYLENEAMILORIDE	6.43
SLC9A1		CARIPORIDE	6.25

Figure 19: Drug-like molecules inhibiting SLC9 transporter

SLC22: Organic cation/anion/zwitterion transporter family

Transporters of the SLC22 family function in different ways. As uniporters that mediate facilitated diffusion in either direction (SLC22A1, SLC22A2, SLC22A3), as anion exchangers (SLC22A6, SLC22A8 and SLC22A12), and as Na^+/L-carnitine cotransporter (SLC22A5). They participate in the absorption and/or excretion of drugs, xenobiotics, and endogenous compounds in intestine, liver and/or kidney, and perform homeostatic functions in brain and heart. Defect mutations of transporters of the SLC22 family may cause specific diseases such as "primary systemic carnitine deficiency" or "idiopathic renal hypouricemia" or change drug absorption or excretion. (21) While urate reabsorption is mostly determined by SLC22A12, this target is one of the most researched in the SLC22 family. Agents and drugs with affinity for SLC22A12 may have paradoxical uricosuric or anti-uricosuric properties when they accumulate in the lumen or within the cell. Prominent inhibitors are several uricosuric or anti-uricosuric drugs including probenecid, benzbromarone, sulfinpyrazone, phenylbutazone, non-steroidal anti-inflammatory drugs, losartan and diuretics. (22)

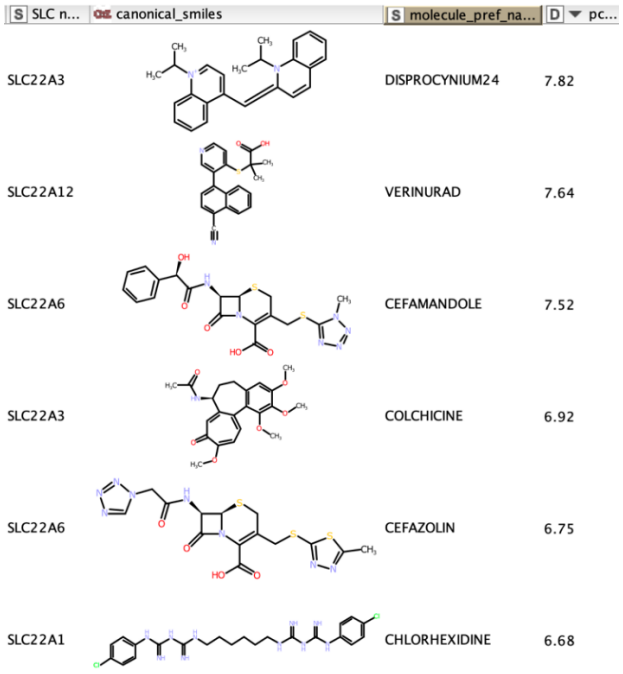


Figure 20: Drug-like molecules inhibiting SLC22 transporter

SLC40: Basolateral iron transporter family

SLC40 is one of these families where only one subfamily is known. SLC40A1, which also can be called “Ferroportin”, is an iron transporter postulated to play a role in intestinal iron absorption and cellular iron release. (23) The protein is most highly expressed in mature enterocytes of the duodenum, in syncytiotrophoblasts, which separate foetal and maternal circulations in the placenta, and in macrophages responsible for recycling iron from breakdown of aged red blood cells. (24)

When SLC40A1 loses function because of mutations, macrophage iron overload and hyperferritinemia are the consequences. (25)

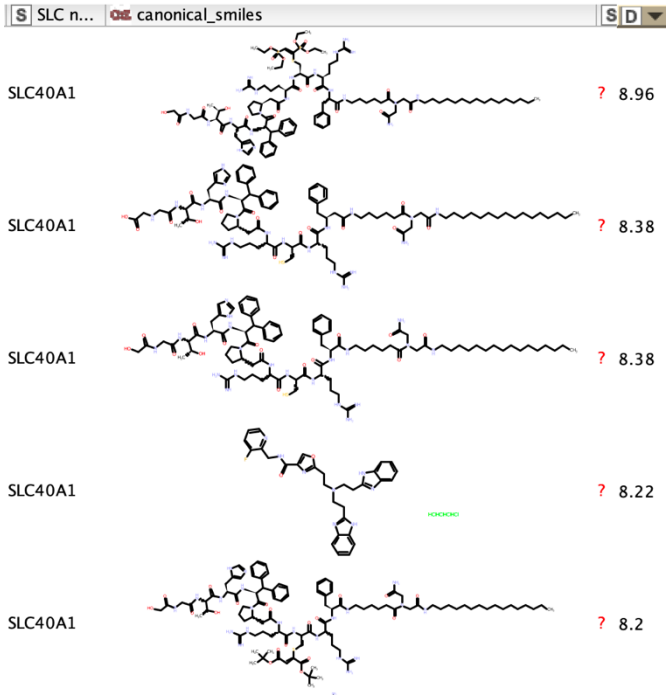


Figure 21: Drug-like molecules inhibiting SLC40 transporter

Orange colored = over 300 counts

SLCO: family of organic anion transporting polypeptides

SLCOs are involved in the membrane transport of bile acids, thyroid hormone, conjugated steroids, eicosanoids, peptides, and numerous drugs in many tissues. (26)

SLCO1B1 and SLCO1B3 make up the majority of targets in this family. For both of this subfamilies, more than 100 inhibitors with a pchembl-value were found. SLCO1B1 turned out to be an important target for statins. Statins, also known as HMG-CoA reductase inhibitors, are a class of lipid-lowering medications for patients with a high risk of cardiovascular disease. They are the most common cholesterol-lowering drugs. SLCO1B1 predominantly is expressed on the membrane of human hepatocytes and is involved in the uptake of various substances from the blood into the liver. In addition to endogenous substances, statins are also substrates of SLCO1B1. Scientists have found that the tolerance of HMG-CoA reductase inhibitors is influenced by variants in the SLCO1B1 gene. (27)

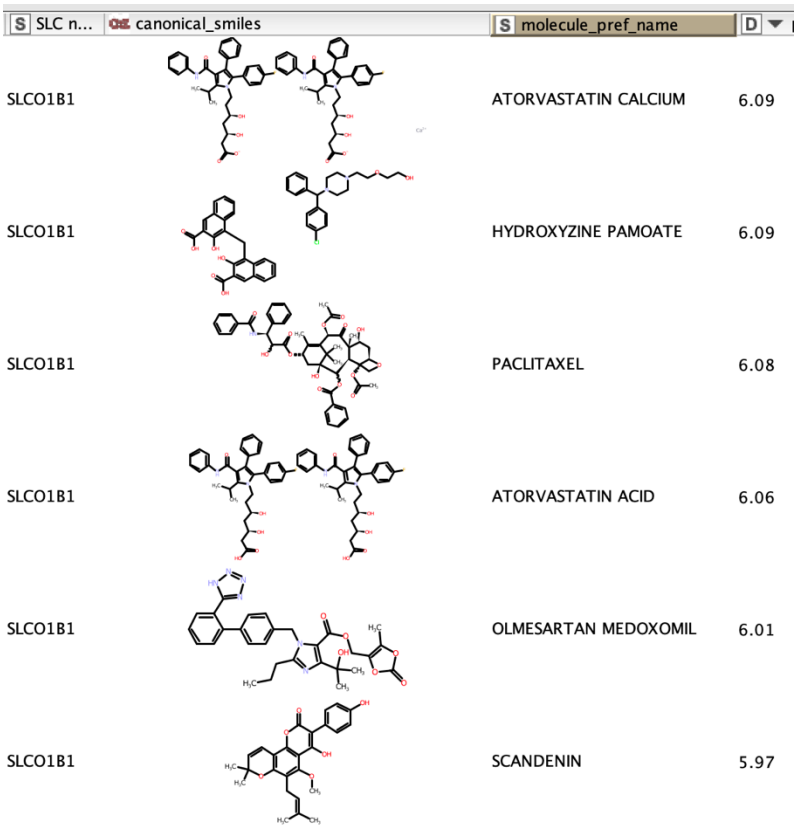


Figure 22: Drug-like molecules inhibiting SLCO transporter

SLC8: Na+/Ca2+ exchanger family

The SLC8 family can be separated into SLC8A1 and SLC8B1, which mediate cellular Ca^{2+} efflux and thus contribute to intracellular Ca^{2+} homeostasis. SLC8A1 is expressed ubiquitously while SLC8B1 is limited to brain and skeletal muscle. SLC8A1 is especially important in regulating cardiac contractility. This transporter mediates the export of Ca^{2+} from the cell during the next phase, so that cytoplasmic Ca^{2+} levels rapidly return to baseline. This is required for normal embryonic heart development and the onset of heart contractions. (28) Scientists found that if SLC8A1 is downregulated while the cGMP-PKG signaling pathway is activated, myocardial damage is alleviated, the release of proinflammatory factors is inhibited and infarct size will be reduced, which ultimately will protect against myocardial damage. (29)

While for SLC8A1 over 300 inhibitors were found, for SLC8B1 only one small molecule with inhibiting potential is available in ChEMBL.

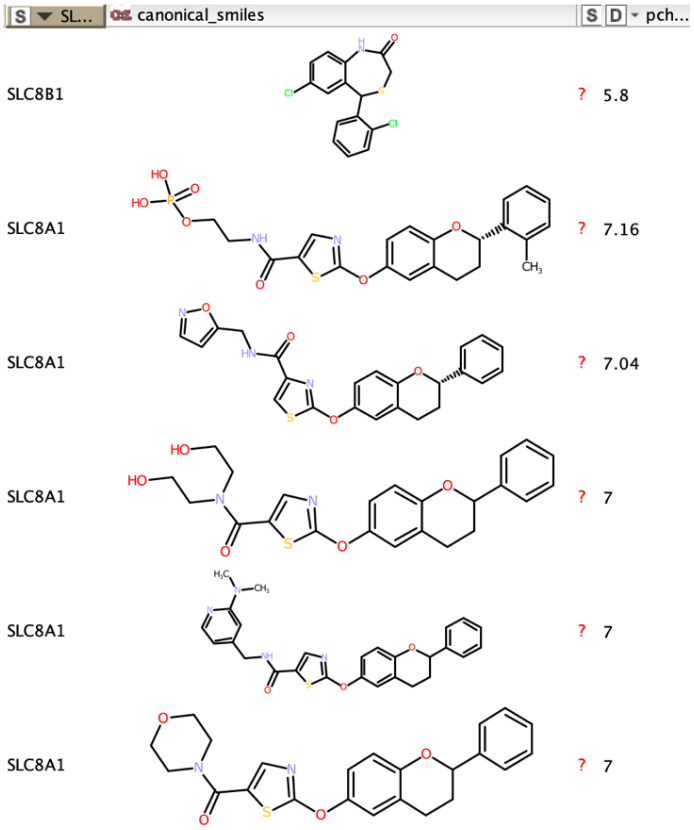


Figure 23: Drug-like molecules inhibiting SLC8 transporter

SLC10: Sodium bile salt cotransport family

The name “Sodium bile salt cotransporter family” is technically obsolete because of the finding of SLC10 members that do not transport bile acids. SLC10A2 plays a key role in cholesterol metabolism because it is reabsorbing bile acids from the lumen of the small intestine. This function is disturbed when patients suffer from intestinal bile acid malabsorption which is leading to a disease called “Morbus Crohn”.

SLC10A1 is primarily situated in hepatocytes and is responsible for the removal of bile acids from the portal circulation. SLC10A1 helps to protect the hepatocyte against increasing intracellular bile acid levels, which will eventually lead to cell damage and apoptosis.

As there are many patients suffering from cholestasis and inflammation, drug discovery for these targets becomes more and more important.

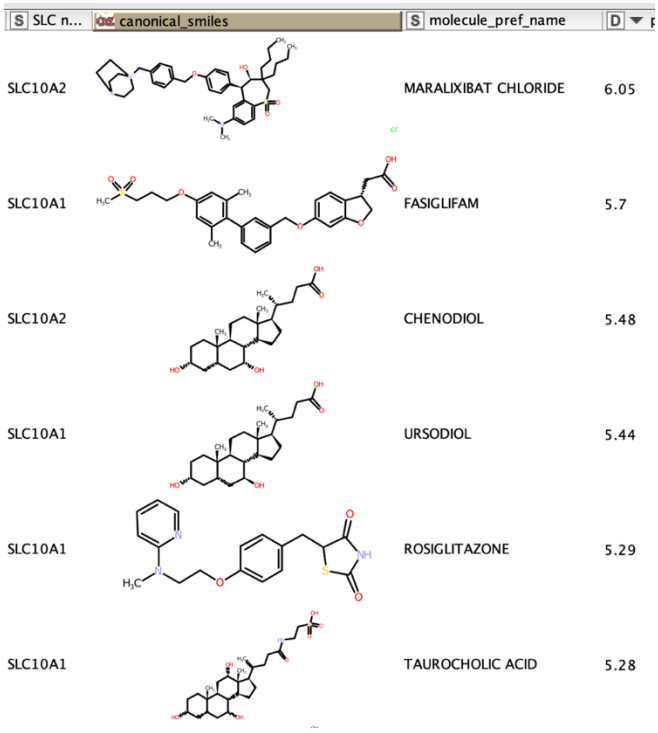


Figure 24: Drug-like molecules inhibiting SLC10 transporter

SLC18: Vesicular amine transporter family

In this family no inhibitors with a pchembl-value were found for SLC18A1. SLC18A3, for which over 100 hits were available in ChEMBL, is carrying acetylcholine into synaptic vesicles and other types of secretory vesicles. SLC18A2 is responsible for transport of monoamines such as dopamine and serotonin. Polymorphisms in SLC18A2 may confer risk for some neuropsychiatric disorders. (30)

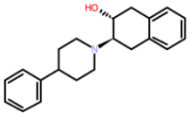
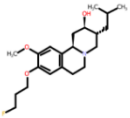
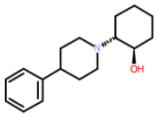
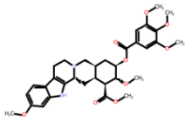
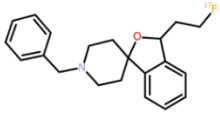
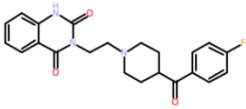
SLC n...	canonical_smiles	molecule_pref_na...	p
SLC18A3		BENZOVESAMICOL	10.26
SLC18A2		FLORBENAZINE	10
SLC18A3		VESAMICOL	8.7
SLC18A2		RESERPINE	8.28
SLC18A3		[18F]FLUSPIDINE	6.68
SLC18A2		KETANSERIN	6.45

Figure 25: Drug-like molecules inhibiting SLC18 transporter

SLC29: Facilitative nucleoside transporter family

Members of the SLC29 family are expressed in the heart, brain, erythrocytes, mammary gland, placenta, in fetal liver and in spleen. They mediate nucleoside influx and efflux and show highest affinity for adenosine. SLC29 transporter can represent a key determinant of the response to treatment with several nucleoside and nucleobase drugs used in cancer chemotherapy and treatment of viral infections, because they promote cellular uptake of nucleosides and nucleobases. (31)

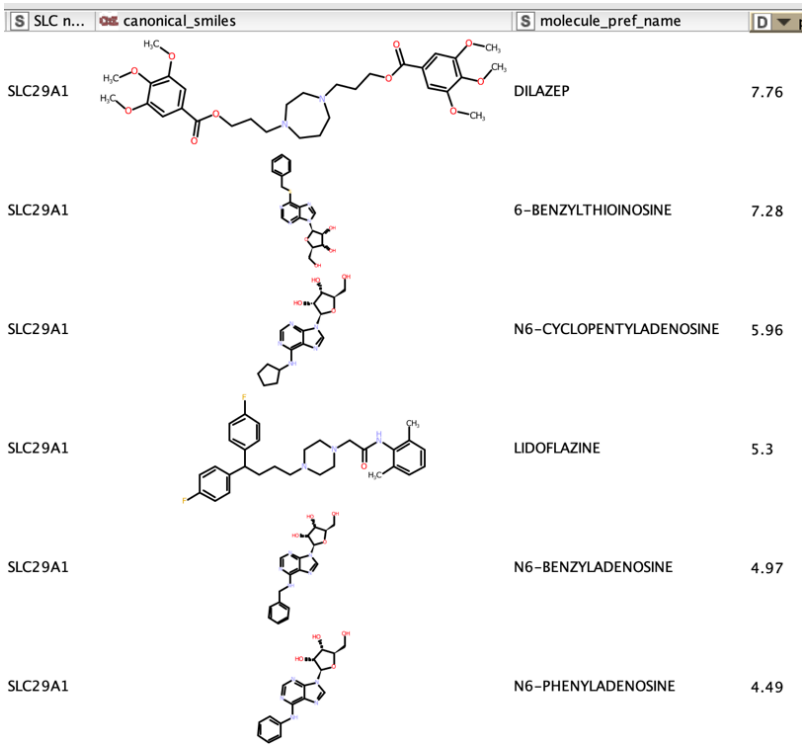


Figure 26: Drug-like molecules inhibting SLC29 transporter

Yellow colored = more than 100 counts

SLC65: NPC-type cholesterol transporters
Especially SLC65A2 is inhibited by many small molecules. SLC65A2, also named as Niemann-Pick C1 Protein, transports low-density lipoproteins to endosomal/lysosomal compartments where they are hydrolyzed and released as free cholesterol. Diseases like Niemann-Pick Disease Type C1 (affects the body's ability to metabolize cholesterol and lipids within cells)
or Headache can be associated with SLC65A2. (32)

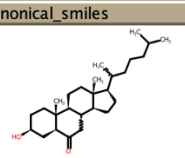
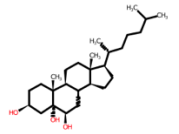
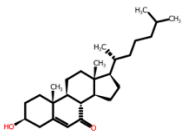
SLC n...	canonical_smiles	molecule_pref_name	pche.
SLC65A2		5alpha-CHOLESTAN-3beta-OL-6-ONE	5.47
SLC65A2		CHOLESTAN-3beta,5alpha,6beta-TRI...	5.77
SLC65A2		7-OXOCHOLESTEROL	5.06

Figure 27: Drug-like molecules inhibiting SLC65 transporter

SLC15: Proton oligopeptide cotransporter family

SLC15A1 can be found in the brush border membrane of the intestinal epithelium and is responsible for the uptake of di- and tripeptides from the lumen into the enterocytes. It plays a main role in the uptake and digestion of dietary proteins. This protein also promotes the absorption of many peptidomimetic drugs. (33)

SLC15A2 is responsible for the absorption of small peptides, as well as beta-lactam antibiotics and other peptide-like drugs, from the tubular filtrate.

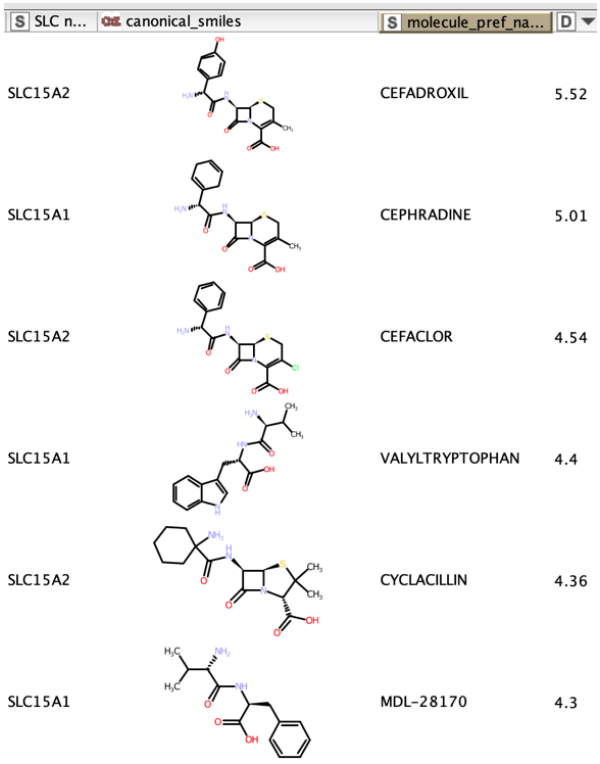


Figure 28: Drug-like molecules inhibiting SLC 15 transporter

SLC16: Monocarboxylate transporter family

Transporter of the SLC16 family are responsible for carrying monocarboxylates such as l-lactate, pyruvate and ketone bodies across the plasma membrane. Because of this, they are involved in a wide range of metabolic pathways including energy metabolism of the brain, skeletal muscle, heart and tumor cells, gluconeogenesis, T-lymphocyte activation, bowel metabolism, pancreatic β-cell malfunction, spermatogenesis, thyroid hormone metabolism, and drug transport. Their potential as pharmacological targets have been recognized with the discovery of potent and specific SLC16A1 inhibitors that act as immunosuppressant drugs by preventing proliferation of T-lymphocytes. It is suggested that the development of other drugs specifically targeting different SLC16 isoforms may provide a novel approach to cancer chemotherapy. (34)

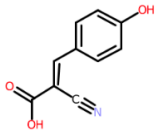
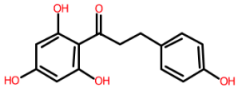
SLC16A3		alpha-CYANO-4-HYDROXYCINNAMIC ACID	4.36
SLC16A3		PHLORETIN	4.39

Figure 29: Drug-like molecules inhibiting SLC16 transporter

SLC33: Acetyl-CoA transporter family

The SLC33 family only contains one subfamily, called SLC33A1. It is primarily located in the pancreas where it imports cytosolic Acetyl-CoA into these organelles.

Knowledge about this transporter is sparse and needs further investigation. What can be noticed when looking at molecules that are inhibiting SLC33A1 is that their inhibiting potency is very high, and the basic chemical scaffold stays the same.

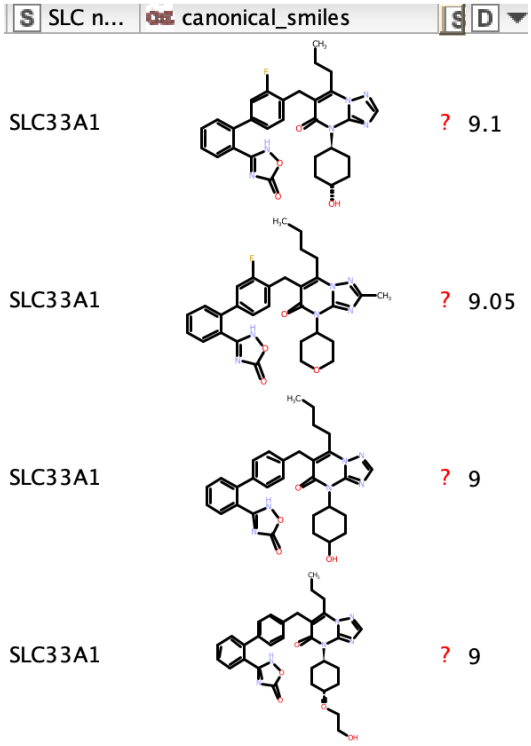


Figure 30: Drug-like molecules inhibiting SLC33 transporter

SLC47: Multidrug and Toxin Extrusion (MATE) family

Transporters of the SLC47 family are responsible for excretion of many drugs in the liver and kidneys and they are localized at the apical membranes of the renal tubules and bile canaliculi.

SLC47A1 and SLC47A2 mediate the secretion of organic cations into urine. They are involved in the excretion of important medications and the disruption of these transporters can cause severe pharmacological problems. Scientists hypothesized that the simultaneous administration of ondansetron during cisplatin treatment enhances the nephrotoxicity associated with cisplatin treatment. This is of interest because during a chemotherapy with cisplatin it is common to give antiemetic 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists, such as ondansetron. (35)

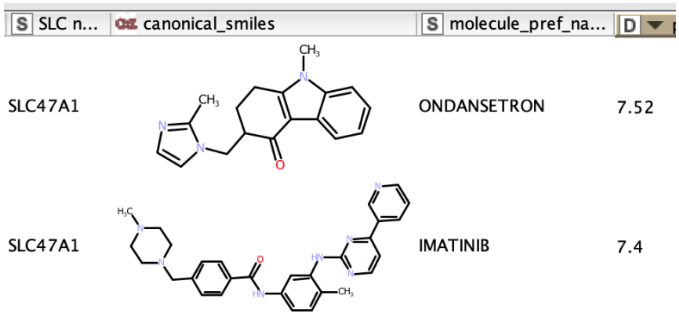


Figure 31: Drug-like molecules inhibiting SLC47 transporter

Blue colored = less than 100 counts

SLC7: Cationic amino acid transporter/glycoprotein-associated family
The SLC7 family is divided into two subgroups, the cationic amino acid transporters (CATs, SLC7A1–4 and SLC7A14) and the L-type amino acid transporters (LATs, SLC7A5-13 and SLC7A15). The SLC7 family is found in all organisms and represents a large family of secondary active transport proteins responsible for uniport, symport and antiport of a broad range of cellular metabolites into and out of the cells. Several genetic disorders are linked to mutations in members of the SLC7 family, including lysinuric protein intolerance and cystinuria, both of which lead to abnormal amino acid transport, growth defects and kidney disease. Several prescription drugs, including L-DOPA and gabapentin are also recognized by members of the SLC7 family, which are expressed in the blood brain barrier and influence the transport and retention of drug molecules into the central nervous system. (36)

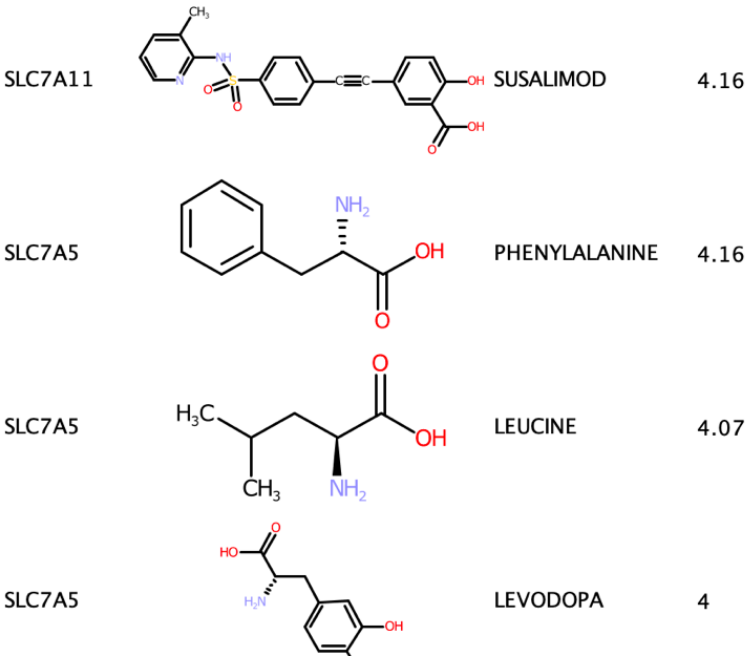


Figure 32: Drug-like molecules inhibiting SLC7 transporter

SLC11: Proton-coupled metal ion transporter family

Only SLC11A2 functions as target for inhibitors with pchembl-value available. In human intestine, uptake of ferrous ion from the diet is mediated primarily by the divalent metal ion transporter, expressed in the brush border membrane of enterocytes in the duodenum. Mutations in the SLC11A2 gene can lead to microcytic anemia. As iron is a key element in the metabolism of almost all living organisms, the availability for oral medication on the luminal side of the intestine makes it an interesting drug target for iron overload disorders. (37)

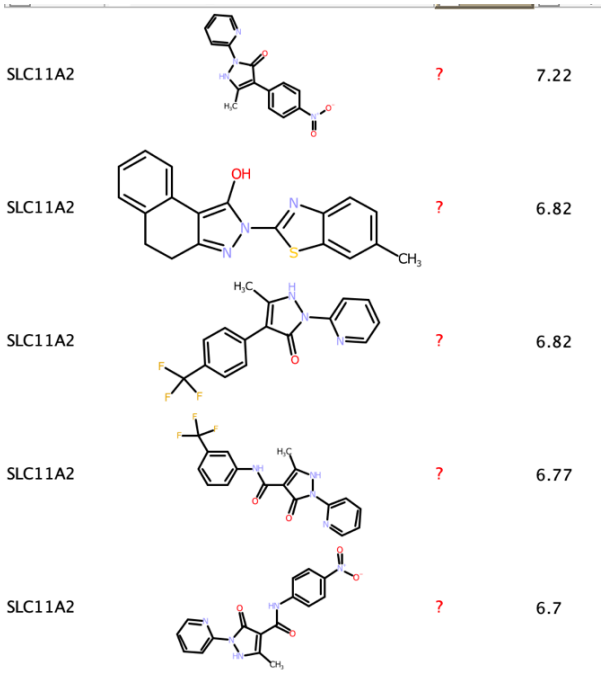


Figure 33: Drug-like molecules inhibiting SLC 11 transporter

SLC12: Electroneutral cation-coupled Cl cotransporter family

The SLC12 family is responsible for several physiological processes like cell volume regulation, modulation of intraneuronal chloride concentration, transepithelial ion movement, and blood pressure regulation. SLC12A2 and SLC12A5 are targets for commonly used diuretic drugs, are causative genes for inherited disease such as Gitelman, Bartter and Andermann syndromes, and potentially play a role in diseases like arterial hypertension, epilepsy, osteoporosis, and cancer. (38)

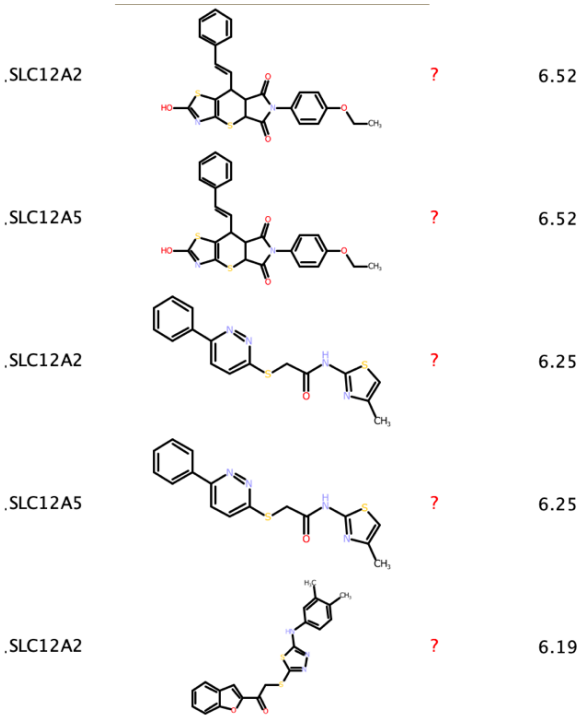


Figure 34: Drug-like molecules inhibiting SLC12 transporter

SLC13: Human Na+-sulfate/carboxylate cotransporter family

The SLC13 transporters are important for regulating plasma, urinary and tissue levels of citrate, succinate, and α-ketoglutarate, which can exert signaling effects through specific receptors or can affect metabolic enzymes directly. SLC13A2, SLC13A3 and SLC13A5 have delivered results as inhibited targets. SLC13A3 is located on the apical membranes of renal proximal tubule and small intestinal cells where it is involved in regulating urinary levels of citrate and plays a role in kidney stone development. SLC13A3 participates in drug and xenobiotic excretion through interactions with organic anion transporters. SLC13A5 is located in the liver and brain where its activity may regulate metabolic processes. (39)

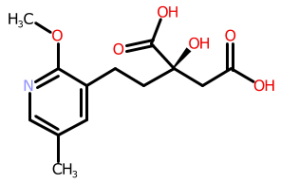
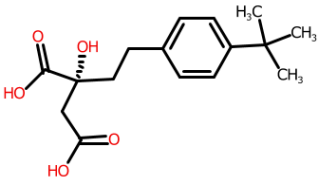
SLC13A3		?	4.85
SLC13A5		?	4.8

Figure 35: Drug-like molecules inhibiting SLC13 transporter

SLC14: Urea transporter family

The SLC14 transporter are primarily responsible for medullary urea accumulation in the urinary concentration process. They are also important in several cellular functions, including urea nitrogen salvaging in the colon, nitric oxide pathway modulation in the hippocampus, and the normal cardiac conduction system. Furthermore, genomic studies have revealed potential roles for SLC14A1 and SLC14A2 in hypertension and bladder carcinogenesis. The precise role of SLC14A1 and it's presence in the urea recycling pathway in normal kidney are issues to be further explored. (40)

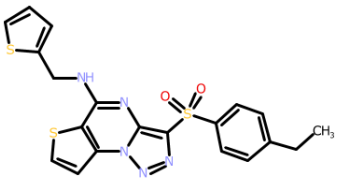
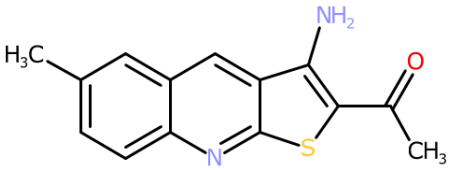
SLC14A1		?	7.96
SLC14A1		?	5.76

Figure 36: Drug-like molecules inhibiting SLC14 transporter

SLC19: Folate/thiamine transporter family and SLC46: Folate transporter family

SLC19A1 and SLC19A2 are expressed ubiquitously and mediate the transport of two important water-soluble vitamins, folate and thiamine.

SLC46A1 is also expressed in the brain and choroid plexus where it transports folates into the central nervous system. This protein further functions as a heme transporter in duodenal enterocytes, and potentially in other tissues like liver and kidney. (41)

Pralatrexate, Methotrexate, Premetrexed and Ralitrexed are inhibitors with high affinity for SLC19A1 and SLC46A1. They are all antineoplastic drugs and function as antifolates. (42)

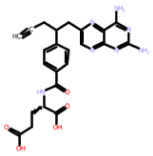
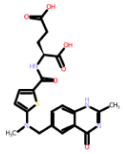
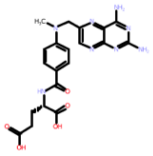
SLC19A1		PRALATREXATE	9.16
SLC19A1		RALTITREXED	8.2
SLC19A1		METHOTREXATE	7.92

Figure 37: Drug-like molecules inhibiting SLC19 transporter

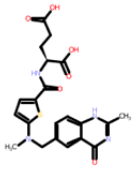
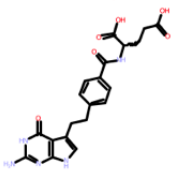
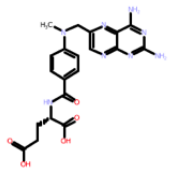
SLC46A1		RALTITREXED	7
SLC46A1		PEMETREXED	6.92
SLC46A1		METHOTREXATE	6.92

Figure 38: Drug-like molecules inhibiting SLC46 transporter

SLC20: Type III Na+-phosphate cotransporter family

SLC20 transporter can be seen as housekeeping transport proteins and are located ubiquitously in all tissues. SLC20A1 regulates dietary phosphate and vitamin D as well as parathyroid hormone secretion from the parathyroid gland. SLC20A2 is involved in intestinal absorption of dietary phosphate.

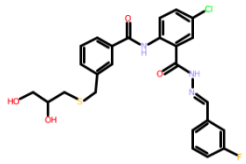
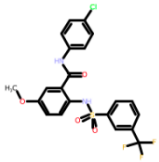
SLC20A1		?	5.27
SLC20A1		?	5.82

Figure 39: Drug-like molecules inhibiting SLC20 transporter

SLC25: Mitochondrial carrier family

This family is with 53 members the largest solute transporter family in humans. These transporters are essential for the functioning of eukaryotes because they carry nutrients across the mitochondrial inner membrane for energy conversion of the cell. Important cellular processes, like oxidative phosphorylation of fats and sugars, amino acid catabolism and interconversion, synthesis of iron sulfur clusters and heme, macromolecular synthesis, and heat production are results afterwards. (43) In the very first output table of "no data found in ChEMBL" can be seen that for a lot of transporters belonging to this family no interaction with small molecules has been measured yet. Only two subfamilies (25A5 and 25A20) are inhibited by drug-like molecules.

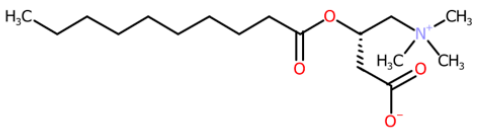
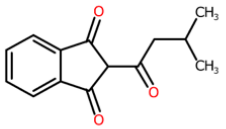
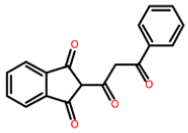
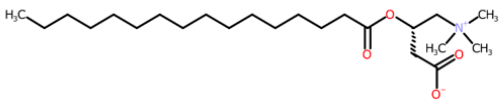
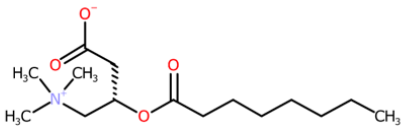
SLC25A20		?	5.3
SLC25A5		?	4.9
SLC25A5		?	4.6
SLC25A20		?	4.46
SLC25A20		?	4.46

Figure 40: Drug-like molecules inhibiting SLC25 transporter

SLC26: Multifunctional anion exchanger family

Transporter belonging to this family facilitate the transport of a variety of organic and inorganic anions. The relevance of the SLC26 family in maintaining anion equilibria is underlined by the causative role of SLC26 proteins in diseases such as congenital chloride diarrhea and cytotoxic brain edema. (44) Only for SLC26A4, inhibitors with pchembl-values were found in ChEMBL.

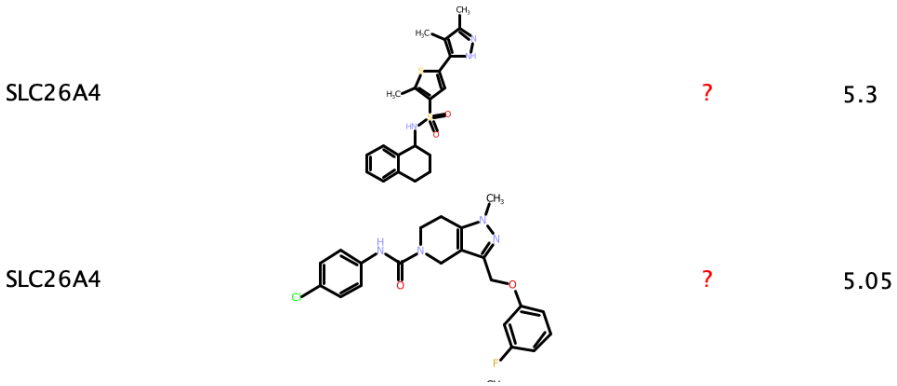


Figure 41: Drug-like molecules inhibiting SLC26 transporter

SLC27: Fatty acid transporter family

The SLC27 family is responsible for carrying long fatty acids through physiological membranes. Especially in heart, intestine, liver and adipose tissue the transport of long-chain fatty acids is regulated and increased by transporters belonging to the SLC27 family. As diseases like type-2 diabetes and acute liver failure can be results of increased fatty acid uptake, these transporters have great potential to function as drug targets for inhibitors. (45)

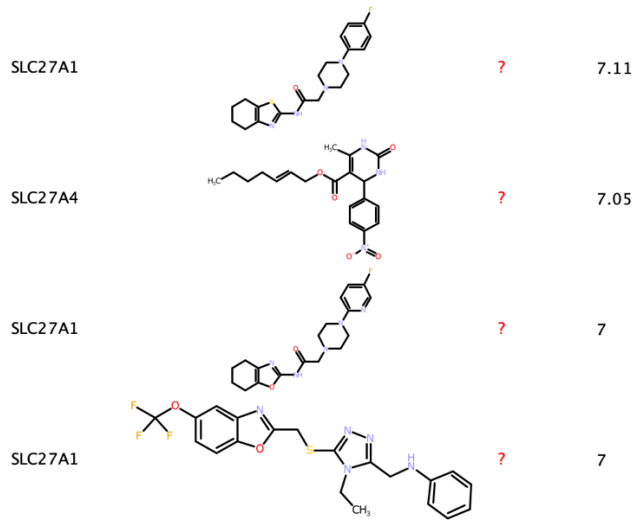


Figure 42: Drug-like molecules inhibiting SLC27 transporter

SLC28: Na+-coupled nucleoside transport family

This family is very similar to the SLC29 family and indeed they work in concert. SLC28 transporters play important roles in nucleoside pathways as they mediate a first step in nucleotide biosynthesis. Both, SLC28 and SLC29 families, terminate adenosine signaling. SLC28 transporter interact with antiviral and anticancer nucleoside analogs by carrying these drugs into target tissues. (46) This important role is a proof that targets like SLC28 transporter, although they are colored blue (what means not much inhibiting-measurements have been made or documented yet), can be of high interest for further research.

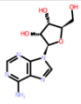
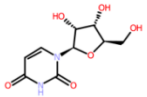
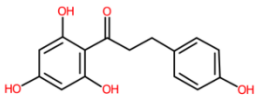
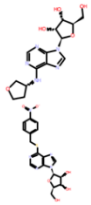
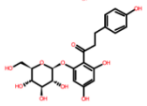
SLC28A1		ADENOSINE	5.26
SLC28A1		URIDINE	5.24
SLC28A3		PHLORETIN	4.49
SLC28A1		TECADENOSON	4.39
SLC28A3		NITROBENZYLMERCAPTOPURINE RIBONUCLEOSIDE	4.05
SLC28A2		PHLORIZIN	4

Figure 43: Drug-like molecules inhibiting SLC28 transporter

SLC34: Type II Na+-phosphate cotransporter family

SLC34A1 and SLC34A3 are particularly expressed in the membrane of the proximal tubule. These transporters are regulated by parathyroid hormone, dietary phosphate status, 1,25-OH2 vitamin D3, acid-base status and electrolyte. Phosphaturia, hypophosphatemia and ectopic organ calcifications are rare diseases related to dysfunctions of SLC34 transporters. (47)

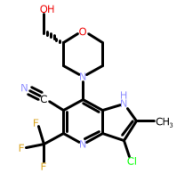
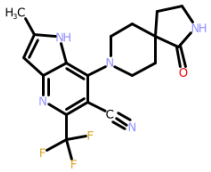
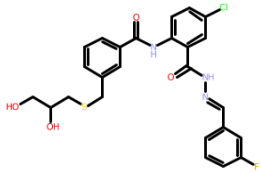
SLC34A1		?	5.89
SLC34A1		?	5.82
SLC34A3		?	5.72

Figure 44: Drug-like molecules inhibiting SLC34 transporter

SLC37: Sugar-phosphate/phosphate exchanger family

For this family, only one transporter is inhibited by small molecules. SLC37A4 can also be named as “G6P transporter”. The name is related to the function of carrying G6P from the cytoplasm into the ER lumen. SLC37A4 is highly selective for Glucose-6-Phosphate and is competitively inhibited by chlorogenic acid and its derivatives. (48) However, research on inhibiting this transporter is not of that great interest as deficiencies of SLC37A4 leads to diseases.

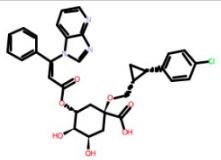
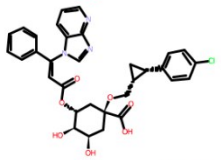
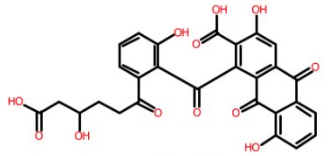
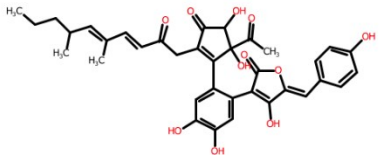
SLC37A4		?	8.7
SLC37A4		?	8.52
SLC37A4		MUMBAISTATIN	8.3
SLC37A4		?	7.1

Figure 45: Drug-like molecules inhibiting SLC37 transporter

SLC43: Na+-independent, system-L-like amino acid transporter family

Only one drug-like inhibitor with a rather low pchembl-value is available in ChEMBL. SLC43A1 is transporting large amino acids and can be associated with Prostate Cancer and Seminoma. The reason for this association is that this transporter is responsible for cellular leucine uptake, and scientists found out that this transporter, such as members of the SLC7 family, show increased expression observed in cancers. (49) Therefor I think it would be of great interest to look at SLC43A1 a bit closer.

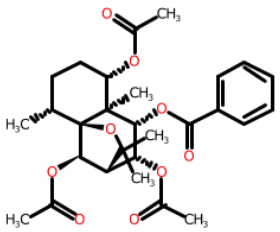
SLC43A1		?	4.81

Figure 46: Drug-like molecule inhibiting SLC43A1

SLC54: Mitochondrial pyruvate carriers

SLC54A2 can be found in the inner mitochondrial membrane and regulates the transport of pyruvate into mitochondria. The findings of SLC54A2 are little but what is known is that a disruption of SLC54A2 (or SLC54A1) results in embryonic lethality. It is also known, as shown below in figure 47, that insulin sensitizers inhibit this transporter. (50)

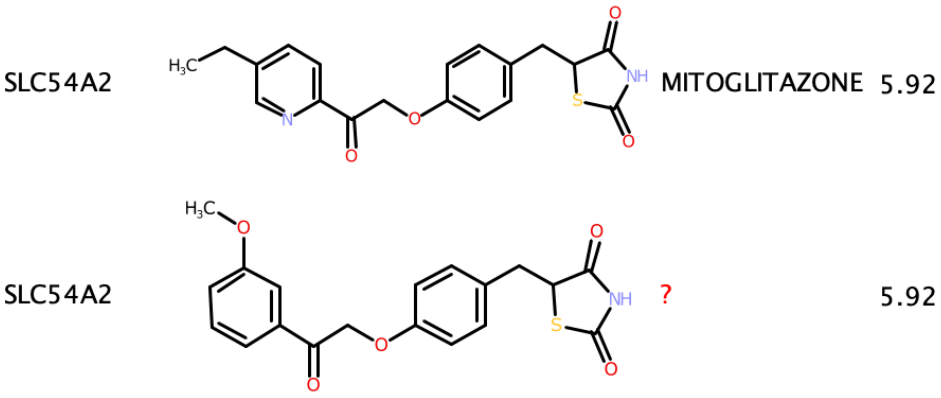


Figure 47: Drug-like molecules inhibiting SLC54A2

Conclusion

SLC-transporter contribute to the large and diverse world of different pathways of molecules in our body. As different as these metabolic pathways can be, the effects of inhibiting them can be equally different. In some cases, it will be desirable to facilitate or accelerate the influx of certain molecules, in other cases the aim might be to inhibit the influx.

In this thesis inhibitors of SLC-transporter were of particular interest. ChEMBL was the suitable database to find SLC related data and obtaining values with which one could do statistical analysis. Creating a workflow in KNIME helped me to keep on track with all these numbers and data outputs. Filtering for measurement-data with a pchembl-value existent should focus on well documented data. Helpful nodes for filtering or calculating median molecular properties further accelerated the work.

Visualizing big data with tables and diagrams generated a good overview and should provide a quick assessment of available data distribution between all the SLC families.

Differences in numbers of hits for SLC families display scientific advances with certain transporter acting as targets, but also areas that still require a lot of research.

Realizing preferred scaffolds based on median molecular properties and already known molecular structures for particular Solute carrier families might help discovering new drugs. Additionally, there can be existent drugs with inhibiting potential for SLC transporter which were actually used for some other purposes.

With the combination of a short definition of the function for each SLC family, the visualization of inhibiting structures with the highest potential and their preferred median molecular properties, I wanted to generate an awareness of some tendency for further research.

In conclusion, it can be said that the world of SLCs still contains a lot of space for research and it is of great importance to invest in this topic, also in families which were disregarded until now.

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