NICEdrug.ch

NICEdrug.ch: workflow for rational drug design and systems-level analysis of drug metabolism

NICEdrug.ch is a resource allowing systematic and large-scale computational analysis of drug biochemistry (metabolic precursors or prodrugs and metabolic fate or degradation), enzymatic targets, and toxicity in the context of cellular metabolism, i.e. currently including: human, *Plasmodium* (malaria parasite), and *E. coli* metabolism.

NICEdrug.ch suggests a new metric for comparison of pairs of molecules that is based on a reactive site-centric fingerprint, the **NICEdrug score**. Furthermore, in NICEdrug.ch the metabolic network analysis of small molecules is coupled with an investigation of their reactive sites. Currently, NICEdrug.ch database incorporates 250,000 bioactive molecules.

NICEdrug.ch

User Manual

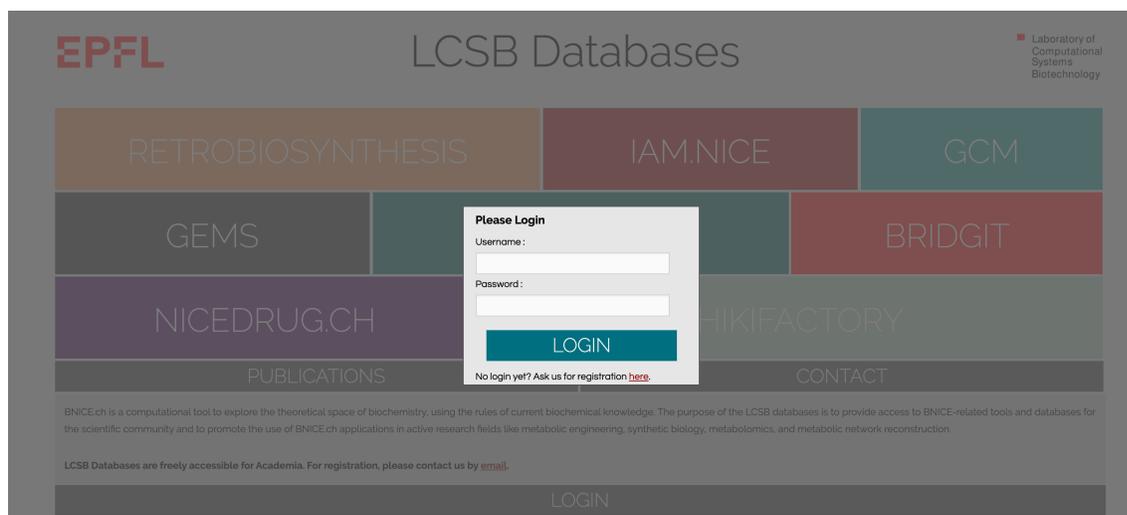## Step1.

Create a user account

Please fill out the online request form:

https://lcsb-databases.epfl.ch/pathways/database_requests

To apply for an academic license, please use your academic email address when registering.

We will send you a license agreement to be signed, and provide your username & password

To log in:

Click on the LOGIN tab at the bottom of the LCSB webpage and insert your login info:
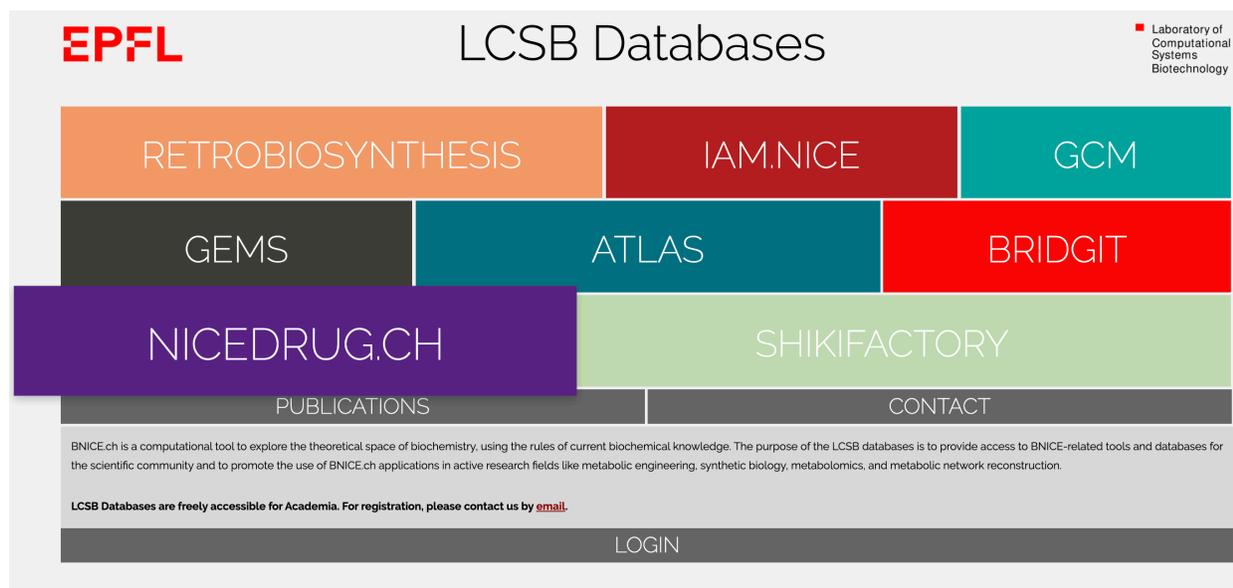

Alternatively, click on any tab within NICEdrug.ch and it will request your login credentials.

Step 2.

Go to the NICEdrug.ch database

You can access the NICEdrug.ch database:

1. By clicking NICEDRUG.CH in the LCSB databases page (see next Figure): https://lcsb-databases.epfl.ch

2. Through the following link: https://lcsb-databases.epfl.ch/Nicedrug

3. Through the following link: NICEdrug.ch

Step 3.

Explore the resources of the NICEdrug.ch database

The NICEdrug.ch database includes (as of today, June 30th of 2020) a set of 250k compounds (compounds list, see below) and an online resource to generate three types of reports to study drug metabolism: (1) Reactivity report, (2) Repurposing report, and (3) Druggability report.

The reports are generated based on a set of defined inputs (see descriptions for each report below).

After submitting a report request, you will be directed to an intermediate page (as shown below), which shows the analysis has started.

Depending on your input parameters, the time to generate the reactivity report will vary between some minutes to some hours.

Please, **keep the generated url (link) to get the results when they are ready**.

If you press the link and your results are ready, your report will be automatically downloaded. If the results are not ready, you will be redirected to a page indicating the results are not ready, and the results will be then automatically downloaded when ready.

The results would be accessible using this url for 1 week and then deleted from our server.

The generated reports are in the format of a downloadable tab-separated file and include embedded links to interact with the NICEdrug.ch database for visualization of compounds and reactions. We recommend using "Numbers" or "Microsoft excel" applications to open the NICEdrug.ch reports.

Compound search

The compound list of NICEdrug.ch comprises the whole set of 250k molecules (as currently available, by June 30th of 2020). The 250k molecules correspond to 50k drugs (whose information has been retrieved and curated from available databases: DrugBank, ChEMBL, KEGG) and 200k metabolic neighbors (putative prodrugs) that are one reaction or step away from the 50k drugs.

How to use it?

You can search the NICEdrug.ch ID of your small molecule of interest in the "Compound search" tab.

Please provide names or identifiers in "Compound name" field or search using the first 14 characters of InChIKey in "InChIKey" field. After pressing "Search" button, it will takes seconds to receive results.

The result in general tab, provide an overview on the matched compound properties. **It is important to note that the LCSB ID (NICEdrug ID) of each molecule is required for the generation of NICEdrug.ch reports** (in the other tabs).

In addition, NICEdrug.ch provides **additional biochemical information** for all molecules including its molecular structure, its predicted metabolic reactions based on the identified reactive sites, and a mapping of external identifiers with direct links.

Downloads

The "Downloads" tab allows to download the compound list in a single table. The downloaded file includes all drugs studied in NICEdrug.ch along with their properties, functions, and target or metabolizing enzymes.

Each molecule has mapped the whole set of identifiers linked to it, including the unique identifier in the NICEdrug database or **NICEdrug ID**, names, the identifiers from others databases in the

corresponding columns (KEGG ID, DrugBank ID, ChEMBL ID). Other information like SMILES, metabolizing enzymes*, target enzyme*, and number of kekulé structures is also available.

The kekulé structures are generated in NICEdrug.ch for aromatic molecules and used in the subsequent NICEdrug.ch analysis.

*Please note that the Information about metabolizing enzymes and target enzymes in the compounds list is based on information available databases (mostly KEGG and ChEMBL) and not on NICEdrug.ch analyses.

1. Reactivity report

The reactivity report identifies *all* reactive sites and target enzymes of known (NICEdrug.ch molecule) or new small molecules in a cell.

Inputs of the **reactivity report** (and if desired a **joint toxicity report**) are:

1) Molecule NICEdrug ID (as available in "compound list" tab)

2) Organism

3) Number of reactions or steps away to generate metabolic neighborhood around input molecule

4) Toxicity analysis: This analysis identifies the reactive site-centric similarity of drugs and their metabolic neighbors with the collection of reference toxic molecules (using the NICEdrug score) and extracts the shared toxic alerts.
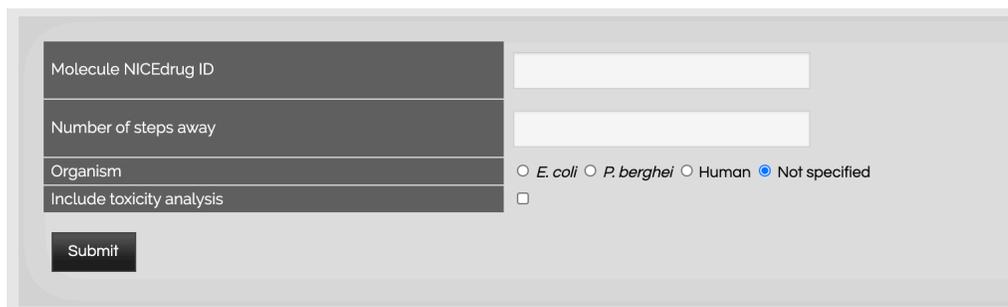
Molecule NICEdrug ID	
Number of steps away	
Organism	○ *E. coli* ○ *P. berghei* ○ Human ● Not specified
Include toxicity analysis	☐
Submit	

Please, insert the inputs into related fields and submit.

As an example, you can generate a **reactivity report for 5-FU** using following input information:

1) Molecule NICEdrug ID: 1467928724

2) Organism: human

3) Number of steps away: 2

4) Include toxicity analysis: yes

After pressing submit you will be directed to the intermediate page, showing the analysis has started. Depending on your input parameters, the time to generate the reactivity report will vary

between some minutes to some hours. **For the reactivity report, a longer time is expected when the number of reaction steps increases or a toxicity analysis is included.**

Please, **keep the generated url (link) to get the results when they are ready**.

If you press the link and your results are ready, your report will be automatically downloaded. If the results are not ready, you will be redirected to a page indicating the results are not ready, and the results will be then automatically downloaded when ready.

The results would be accessible using this url for 1 week and then deleted from our server.

The reactivity report includes information about the metabolism of the input small molecule, and (if requested) its toxicity report.

Output (headers and descriptions) of the **reactivity report** are the followings:

- "input_molecule_name": name of input molecule
- "input_molecule_NICEdrug_ID": NICEdrug ID of input molecule
- "input_molecule_link_NICEdrug.ch": link for visualization of input molecule in NICEdrug.ch
- "#steps_away": number of reactions away from input molecule
- "substrate_name": name of substrate molecule (it is the input molecule if the step away is one)
- "substrate_NICEdrug_ID": NICEdrug ID of substrate molecule
- "substrate_link_NICEdrug.ch": link for visualization of substrate in NICEdrug.ch
- "product_name": name of product molecule
- "product_SMILES": SMILES structure of product molecule
- "product_drugBank_ID": ID of product molecule in DrugBank
- "product_KEGG_ID": ID of product molecule in KEGG
- "product_ChEMBL_ID": ID of product molecule in ChEMBL
- "product_FooDB_ID": ID of product molecule in FooDB
- "product_NICEdrug_ID": ID of product molecule in NICEdrug.ch

- "product_link_NICEdrug.ch": link for visualization of product in NICEdrug.ch

- "EC|Enzymatic_Rule": EC number and BNICE enzymatic rule corresponding to substrate-product biotransformation

- "substrate/product_NICEdrug_ID": ID of substrate-product reaction pair in NICEdrug.ch

- "substrate/product_link_NICEdrug.ch": link for visualization of substrate/product reaction pair in NICEdrug.ch

- "conserved_atom_ratio": ratio of atoms conserved between substrate and product

Output (headers and descriptions) of the **toxicity report** are the followings:

- "molecule_name": name of input molecule or its neighboring molecules (as present in the reactivity report)

- "molecule_NICEdrug_ID": NICEdrug ID of input molecule or its neighboring molecules (as present in the reactivity report)

- "molecule_link_NICEdrug.ch": link for visualization of input molecule or its neighboring molecules in NICEdrug.ch

- "Most_similar_hep_name": name of the most similar hepatotoxic molecule (H)

- "Most_similar_hep": NICEdrug ID of the most similar hepatotoxic molecule (H)

- "Most_similar_hep_link_NICEdrug.ch": link for visualization of the most similar hepatotoxic molecule (H) in NICEdrug.ch

- "Most_similar_sup_name": name of the most similar supertoxic molecule (S)

- "Most_similar_sup": NICEdrug ID of the most similar supertoxic molecule (S)

- "Most_similar_sup_link_NICEdrug.ch": link for visualization of the most similar supertoxic molecule (S) in NICEdrug.ch

- "hep_NICEdrug_score", " sup_NICEdrug_score": NICEdrug score (to H or S)

- "hep_#_alerts", " sup_#_alerts": number of shared structural alerts (with H or S)

- "hep_SMART_alerts", " sup_SMART_alerts": SMART pattern of shared structural alerts (with H or S)

- "hep_alerts_des", " sup_alerts_des": description of shared structural alerts (with H or S)

- "hep_alerts_ID"," sup_alerts_ID": IDs of shared structural alerts with (H or S)

2. Repurposing report

The repurposing report identifies drugs for repurposing to target an enzyme in a cell.

Inputs of the **repurposing report**:

    1) Molecule NICEdrug ID (as available in "compound list" tab)

    2) Organism

Please, insert the inputs into related fields and submit.

As an example, you can generate a **repurposing report for Lovastatin acid** (a statin molecule) using following input information:

    1) Molecule NICEdrug ID: 1468050454

    2) Organism: human

After pressing submit you will be directed to the intermediate page, showing the analysis has started. Depending on your input parameters, the time to generate the repurposing report will vary between some minutes to some hours. **For the repurposing report, a longer time is expected when the complexity of the input molecules and number of reactive sites on it increases.**

Please, **keep the generated url (link) to get the results when they are ready**.

If you press the link and your results are ready, your report will be automatically downloaded. If the results are not ready, you will be redirected to a page indicating the results are not ready, and the results will be then automatically downloaded when ready.

The results would be accessible using this url for 1 week and then deleted from our server.

The repurposing report includes all alternative small molecules (in NICEdrug.ch) that can inhibit the same enzymes as the input small molecule.

Output (headers and descriptions) of the **repurposing report** are the followings:

- "input_molecule_name": name of input molecule
- "input_molecule_NICEdrug_ID": NICEdrug ID of input molecule
- "input_molecule_link_NICEdrug.ch": link for visualization of input molecule in NICEdrug.ch
- "BNICE_enzymatic_rule": target inhibited enzyme 3th level E.C., as defined in a BNICE enzymatic rule
- "similar_molecule_name": name of similar molecule
- "similar_molecule_SMILES": SMILES structure of similar molecule
- "similar_molecule_drugBank_ID": ID of similar molecule in DrugBank
- "similar_molecule_KEGG_ID": ID of similar molecule in KEGG
- "similar_molecule_ChEMBL_ID": ID of similar molecule in ChEMBL
- "similar_molecule_FooDB_ID": ID of similar molecule in FooDB
- "similar_molecule_NICEdrug_ID": ID of similar molecule in NICEdrug.ch
- "similar_molecule_link_NICEdrug.ch": link for visualization of similar molecule in NICEdrug.ch
- "NICEdrug_score": NICEdrug score between input molecule and similar molecule with respect to the reactive site identified by the target enzyme

3. Druggability report

The druggability report identifies inhibitors (drugs or prodrugs) of an input enzyme and cell.

Input of the **druggability report** is the E.C. number of the enzyme to be targeted (3th or 4th level E.C.)

Please, insert the input into related fields and submit.

As an example, you can generate a **druggability report for oxidoreductases** (acting on the CH-OH group of donors, with oxygen as acceptor) using following input information (which is a 3th level E.C.):

     1) EC number: 1.1.3

After pressing submit you will be directed to the intermediate page, showing the analysis has started. Depending on your input parameters, the time to generate the intermediate druggability report will take some minutes. **Press the link and your report will be automatically downloaded. The results would be accessible using this url for 1 week** and then deleted from our server.

The **druggability report** includes information of all candidate small molecules that target or inhibit the input enzyme (EC) following the mechanism of reactions it catalyzes.

Output (headers and descriptions) of the **druggability report** are the followings:

- "substrate_name": name of substrate
- "substrate_NICEdrug_ID": ID of substrate in NICEdrug.ch
- "substrate_link_NICEdrug.ch": link for visualization of substrate in NICEdrug.ch
- "BNICE_enzymatic_rule": BNICE enzymatic rule corresponding to the target or inhibited enzyme

- "similar_molecule_name": name of similar molecule targeting the same enzyme (candidate small molecule)

- "similar_molecule_SMILES": SMILES structure of similar molecule

- "similar_molecule_drugBank_ID": ID of similar molecule in DrugBank

- "similar_molecule_KEGG_ID": ID of similar molecule in KEGG

- "similar_molecule_ChEMBL_ID": ID of similar molecule in ChEMBL

- "similar_molecule_FooDB_ID": ID of similar molecule in FooDB

- "similar_molecule_NICEdrug_ID": ID of similar molecule in NICEdrug.ch

- "similar_molecule_link_NICEdrug.ch": link for visualization of similar molecule in NICEdrug.ch

- "NICEdrug_score": NICEdrug score between substrate and similar molecule with respect to the reactive site identified by the target enzyme

Other functions

In this tab, you can access directly two functions that are used in the generation of NICEdrug.ch reports and they can be useful independently.

1. NICEdrug score between two compounds

The function of **NICEdrug score between two compounds**, provides reactive site centric similarity score between two input molecules.

Inputs of this function are:

1) The first molecule NICEdrug ID (as available in "compound list" tab)

2) The second molecule NICEdrug ID (as available in "compound list" tab)

Please, insert the inputs into related fields and submit.

As an example, you can generate reactive site centric similarity scores between cladribine and Deoxyguanosine using following input information:

　　　1) The first molecule NICEdrug ID =1468100787

　　　2) The second molecule NICEdrug ID =1467869751

After pressing submit you will be directed to the intermediate page, showing the analysis has started. Depending on your input parameters, the time to generate the output file will vary between some seconds to some minutes.

Please, **keep the generated url (link) to get the results when they are ready**.

If you press the link and your results are ready, your output file will be automatically downloaded.

If the results are not ready, you will be redirected to a page indicating the results are not ready, and the results will be then automatically downloaded when ready.

The results would be accessible using this url for 1 week and then deleted from our server.

Output (headers and descriptions) of the function of **NICEdrug score between two compounds** are the followings:

- "molecule1_NICEdrug_ID": NICEdrug ID of input molecule

- " enzymatic_rule": 3th level E.C., as defined in a BNICE enzymatic rule

- "molecule2_NICEdrug_ID": ID of similar molecule in NICEdrug.ch

- "NICEdrug_score": NICEdrug score between 2 molecules with respect to the reactive site identified by the enzymatic rule

2. Scanning compounds with structural alerts

This function, is used in toxicity evaluation of molecules in the reactivity report. Here, you can directly access it. This functions checks if structural alerts exit on input molecule.

Inputs of this function is:

　　　1) The molecule NICEdrug ID (as available in "compound list" tab)

Please, insert the input into related field and submit. As an example, you can scan 5-fu molecule using following input information:

      1) The molecule NICEdrug ID = 1467928724

After pressing submit you will be directed to the intermediate page, showing the analysis has started. Depending on your input parameters, the time to generate the output file will vary between some seconds to some minutes.

Please, **keep the generated url (link) to get the results when they are ready**.

If you press the link and your results are ready, your output file will be automatically downloaded.

If the results are not ready, you will be redirected to a page indicating the results are not ready, and the results will be then automatically downloaded when ready.

The results would be accessible using this url for 1 week and then deleted from our server.

Output (headers and descriptions) of the function of **scanning compounds with structural alerts** are the followings:

- " alert ID ": ID of alerts according to OCHEM database.
- "alert description": Explaining the reason why the alert is toxic
- "SMART pattern of alert": Toxic substructure in the format of SMART
- " #occurrence of alert ": How many of substructures on the molecule, map the alert SMART formula

How to cite NICEdrug.ch:

Please cite the following reference for using NICEdrug.ch:

Homa MohammadiPeyhani, Anush Chiappino-Pepe,Kiandokht Haddadi,

Jasmin Hafner, Noushin Hadadi, Vassily Hatzimanikatis. Database for drug metabolism and

comparisons, NICEdrug.ch, aids discovery and

design.bioRxiv 2020.05.28.120782; doi: https://doi.org/10.1101/2020.05.28.120782