



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.

User Manual

Step1.

Create a user account

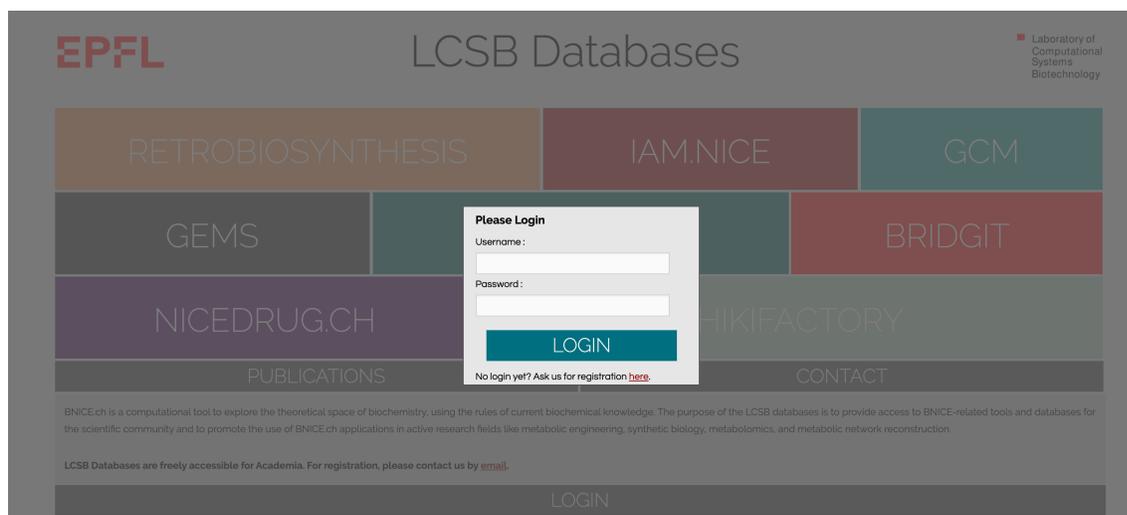
Please fill out the online request form:

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:



The screenshot shows the LCSB Databases website interface. At the top left is the EPFL logo, and at the top center is the text "LCSB Databases". On the top right, it says "Laboratory of Computational Systems Biotechnology". The main content area features several database categories: RETROBIOSYNTHESIS, IAM.NICE, GCM, GEMS, BRIDGIT, NICE DRUG.CH, and SHIKIFACTORY. At the bottom, there are links for PUBLICATIONS and CONTACT. A "Please Login" modal form is centered over the page, containing fields for "Username:" and "Password:", a "LOGIN" button, and a link: "No login yet? Ask us for registration [here](#)". At the very bottom of the page, there is a "LOGIN" tab.

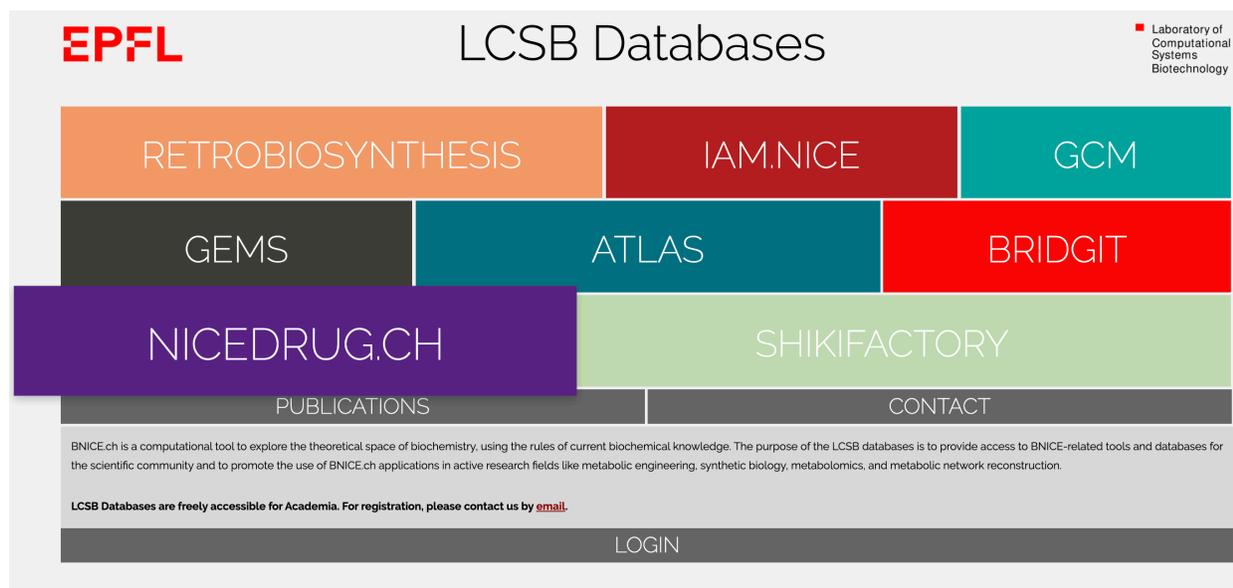
Alternatively, click on any tab within NICEdrug.ch and it will request your login credentials.

Step 2.

Go to the NICEdrug.ch database

You can access the NICEdrug.ch database:

1. By clicking NICE DRUG.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



The screenshot shows the 'LCSB Databases' website interface. At the top left is the EPFL logo. The title 'LCSB Databases' is centered at the top. On the top right, it says 'Laboratory of Computational Systems Biotechnology'. Below the title is a grid of database categories: RETROBIOSYNTHESIS (orange), IAM.NICE (dark red), GCM (teal), GEMS (dark grey), ATLAS (teal), BRIDGIT (red), NICE DRUG.CH (purple), and SHIKIFACTORY (light green). Below this grid are two buttons: PUBLICATIONS and CONTACT. A paragraph of text describes the purpose of the databases. At the bottom, there is a LOGIN button and a note: 'LCSB Databases are freely accessible for Academia. For registration, please contact us by email.'

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.



The screenshot shows the NICEdrug.ch website interface. At the top left is the EPFL logo. In the center is the NICEdrug.ch logo. On the top right is the Laboratory of Computational Systems Biotechnology logo. Below the logos is a navigation menu with links: HOMEPAGE, NICE DRUG.CH, COMPOUND LIST, REACTIVITY REPORT, REPURPOSING REPORT, DRUGGABILITY REPORT, and OTHER FUNCTIONS. The main content area displays a message: "NICEdrug analysis" followed by "The analysis has been launched. Please keep the following URL to get the results: https://lcsb-databases.epfl.ch/Nicedrug/GetResults/6749004". At the bottom of the page, there is a footer: "© 2014-2020 LCSB - EPFL No login yet? Send us an [email](#)".

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 screenshot shows the NICEdrug.ch website interface. At the top left is the EPFL logo. The main title is NICEdrug.ch. On the right, it says "Laboratory of Computational Systems Biotechnology". Below the title is a navigation menu with options: HOMEPAGE, NICE DRUG.CH, COMPOUND SEARCH (highlighted in purple), REACTIVITY REPORT, REPURPOSING REPORT, DRUGGABILITY REPORT, and OTHER FUNCTIONS. Below the navigation is a "DOWNLOADS" link. The main search area contains three input fields: "Compound Name" (with "tylenol" entered), "Compound ID", and "InChIKey". Below these fields is a "Search - please be patient :)" button.

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).**

Compound Name:

Compound ID:

InChIKey:

General | Reactions | Database Links | Structure

LCSB ID	1467921436
Names	Acetaminophen
InChIKey	RZVAJINKPMORJF-UHFFFAOYSA-N
SMILES	CC(=O)Nc1ccc(cc1)O
Molecular formula	C8H9NO2
Energy (kcal/mol)	NaN
Error	NaN
Molecular weight	151.16

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.

Compound Name:

Compound ID:

InChIKey:

General | Reactions | **Database Links** | Structure

Database	Identifiers
KEGG	C06804 , D00217
SEED	cpd04176
MetaNetX	MNXM1944 , MNXM1944
MetaCyc	CPD-7669
PubChem	1983 , 131869277
ChEBI	46195
ChEMBL	CHEMBL112

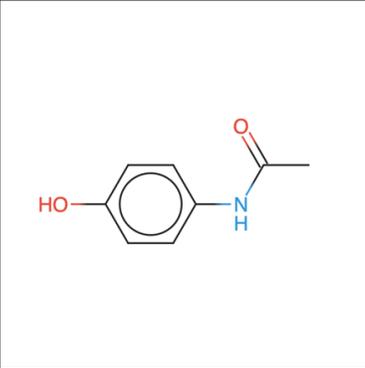
Compound Name:

Compound ID:

InChIKey:

General Reactions Database Links **Structure**

Compound structure



Compound Name:

Compound ID:

InChIKey:

General **Reactions** Database Links Structure

98 reactions found for compound **1467921436**

LCSB ID (refV)	Reaction equation	Reaction rule	EC number	Database links	Reactant pairs	Conserved Atomic Ratios (CARs)	Energy (kcal/mol)	Error
1557005898	H+ + 1467991745 + Oxygen + (2) NADPH <=> (2) NADP+ + 1467879788 + H2O + 1467921436	1.14.13B1						
1557008397	1467991745 + H2O <=> 1467879788 + 1467921436	3.8.1A2			1467991745 1467921436 1467991745 1467879788 1467921436 H2O	0.9 0.04 0.04		
1559405462	H+ + 1467921436 + NADH <=> 165515902 + NAD+	1.2.1B1(rev)			1467921436 165515902 NADH NAD+	1 1	10.54	0.050008
1559405480	H+ + 1467921436 + NADPH <=> 165515902 + NADP+	1.2.1B2(rev)			1467921436 165515902 NADPH NADP+	1 1	10.54	0.050214
1559405498	H+ + 1467921436 + NADH <=> 651753119 + NAD+	1.3.1A1(rev)			1467921436 651753119 NADH NAD+	1 1	10.92	0.289535
1559405499	H+ + 1467921436 + NADH <=> 651753119 + NAD+	1.3.1A1(rev)			1467921436 651753119 NADH NAD+	1 1	10.92	0.289535

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.

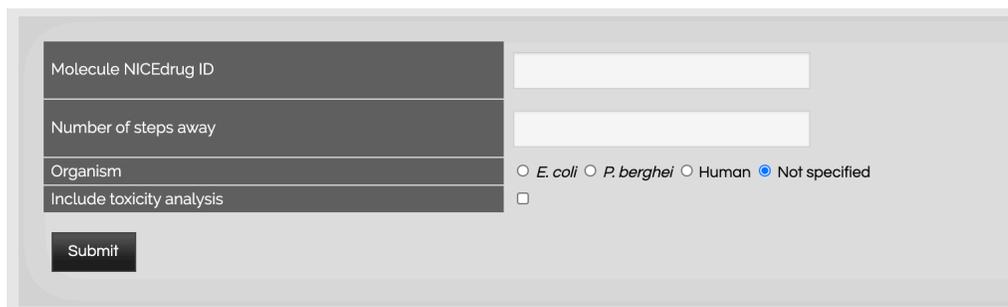
*Please note that the Information about metabolizing enzymes and target enzymes in the compounds list is based on information available databases (mostly KEGG and ChEMBL) and not on NICEdrug.ch analyses.

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.



The screenshot shows a web form with the following fields and options:

- 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



The screenshot shows a web form with two input fields: 'Molecule NICEdrug ID' and 'Organism'. The 'Organism' field has radio button options for 'E. coli', 'P. berghei', 'Human', and 'Not specified', with 'Not specified' selected. A 'Submit' button is located on the right side of the form.

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.)



The screenshot shows a web form with a dark grey header. On the left, there is a dark grey label 'EC number' next to a white input field. On the right, there is a dark grey button labeled 'Submit'.

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)

NICEdrug score between two compounds

<div style="display: flex; align-items: center;"> <div style="background-color: #444; color: white; padding: 2px 5px; font-size: 0.8em; margin-right: 5px;">Molecule 1 NICEdrug ID</div> <input style="width: 90%; border: 1px solid #ccc;" type="text"/> </div>	<div style="display: flex; align-items: center;"> <div style="background-color: #444; color: white; padding: 2px 5px; font-size: 0.8em; margin-right: 5px;">Molecule 2 NICEdrug ID</div> <input style="width: 90%; border: 1px solid #ccc;" type="text"/> </div>	<input style="background-color: #444; color: white; padding: 5px 10px; border: none;" type="submit" value="Submit"/>
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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)



The screenshot shows a web form titled "Scanning compounds with structural alerts". It contains a single text input field with the placeholder text "Molecule NICEdrug ID" and a "Submit" button to its right.

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>