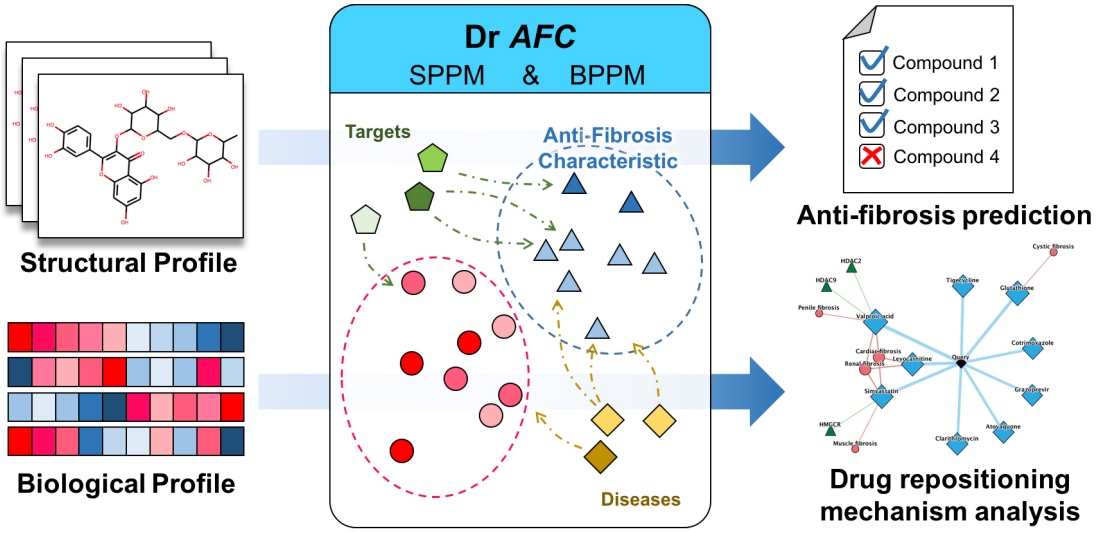
Tutorial

Content

Overview

Dr *AFC* (https://www.biosino.org/drafc/) is a comprehensive, freely accessible platform aimed for Drug Repositioning that is based on anti-fibrosis characteristic and a virtual Knowledge Base accommodating anti-fibrosis compounds, targets and their interactions. Dr *AFC* provides two main functions, anti-fibrosis prediction and drug repositioning mechanism analysis. Through Dr *AFC* platform, anti-fibrosis and potential repositioning could be predicted from compound structures and/or biological profiles. Drug repositioning mechanism analysis could infer the relationships among compounds, fibrosis-related targets and fibrotic diseases which help researchers understand pathology. Furthermore, druglikeness estimation, chemical similarity calculation and structure matching were integrated into Dr *AFC* to provide more useful information for drug development.



1. Anti-fibrosis Knowledge Base

Dr *AFC* constructed the **Anti-fibrosis Knowledge Base** based on anti-fibrosis related literatures and clinical trials. Literatures from PubMed were collected through the key word "*fibrosis AND target*" in PubMed from Jan. 1st, 2000 to Oct. 31st, 2019. Literatures from Comparative Toxicogenomics Database (CTD)[1] were collected through the disease category "*fibrosis*" from Jan. 1st, 2000 to Oct. 31st, 2019. Clinical trials from ClinicalTrials.gov[2] were collected through the key word "*fibrosis*" from Jan. 1st, 2000 to Oct. 31st, 2019. In addition, approved anti-fibrosis drugs from DrugBank (Version 5.1.3) [3] were collected. Anti-fibrosis treatments, fibrosis-related targets and compound-target information were extracted from collected literatures and trials. Statistics of all items are shown below (Table 1).

Table 1. The numbers of Dr AFC records.

Type	**Counts**
Anti-fibrosis Treatments	1223
Fibrosis-related Targets	1067
Fibrosis-related References	3096

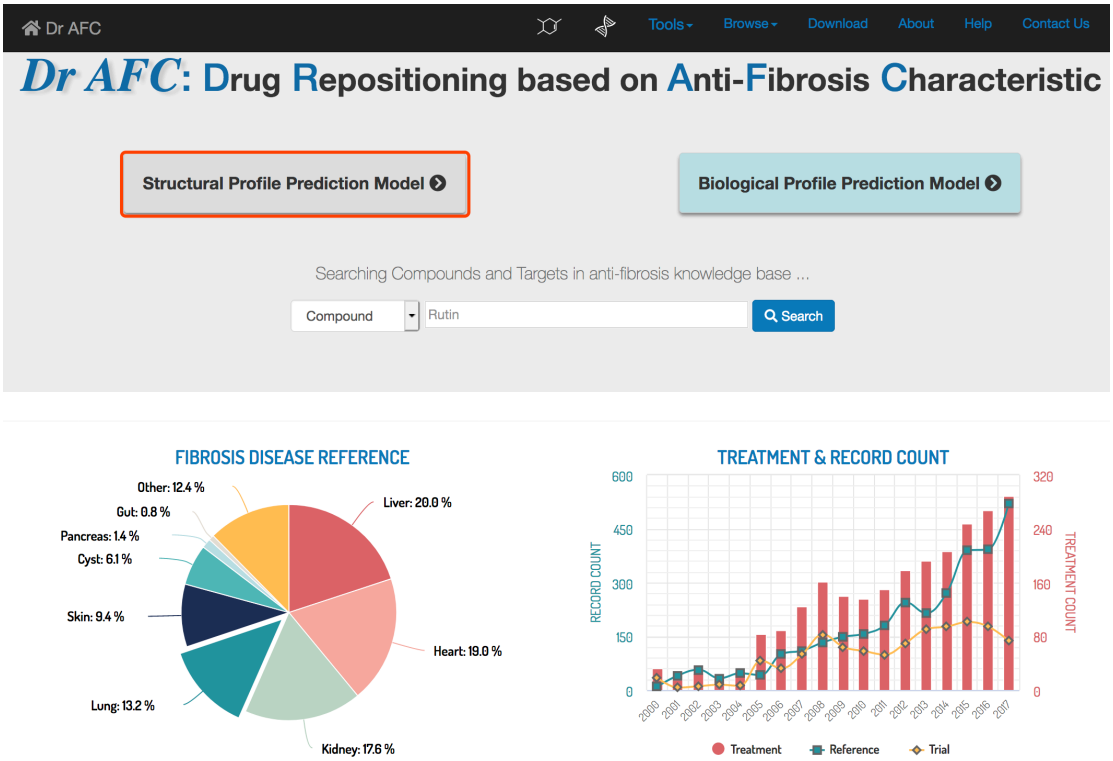
Fibrosis-related Clinical Trials	1787
Fibrosis-related Compound-Target Interactions	507

2. Drug Repositioning based on Structural Profile Prediction Model(SPPM)

The **SPPM** of Dr AFC could calculate anti-fibrosis and repositioning score(S) using structural profile. The anti-fibrosis and repositioning score reflect the ability of a compound serving as a therapeutic treatment for fibrotic diseases. The model was constructed based on gradient boosting method. The optimal feature set used in modelling was selected by Iterative feature elimination (IFE) algorithm. SMILES strings of compounds would be submitted to **SPPM** and Dr AFC will return repositioning results accordingly.

1) Enter the **SPPM** page

From our homepage, click the **Structural Profile Prediction Model** to enter the **SPPM** submission page.



2) Submit compound structure

SPPM accepts compound structures in two ways and users can choose either of them.

A. Enter or paste compound name followed by its SMILES string in the input box. Compound name and its corresponding SMILES string should be separated by a Tab, comma or space character.

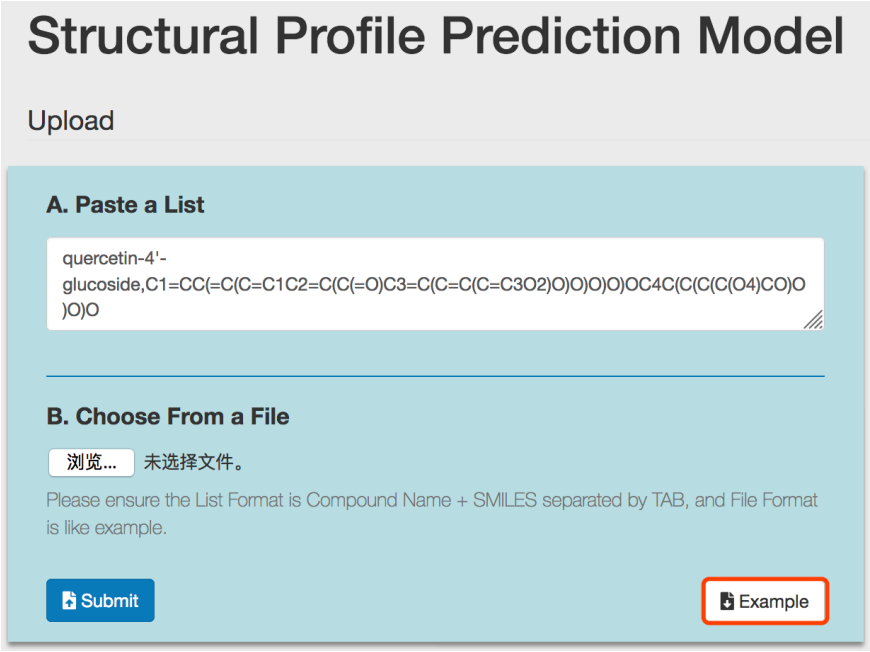
e.g.

quercetin-4'-glucoside,C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)OC4C(C(C(C(O4)CO)O)O)O

Multiple compounds are also allowed, with each compound in a separate row.

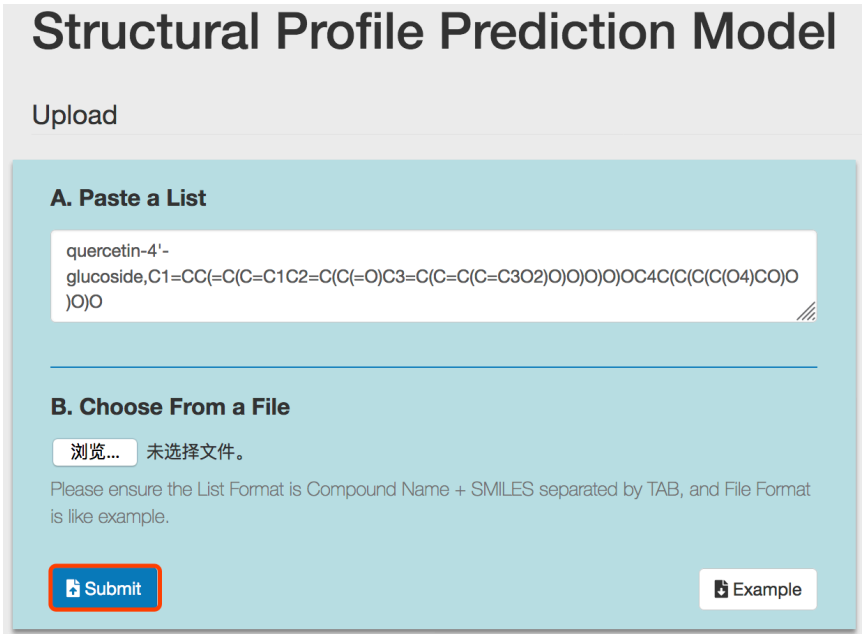
B. Upload a file containing compound names followed by their SMILES strings. The file should

have two columns, compound names and corresponding SMILES strings. The two columns should be separated by a Tab, comma or space character. File format could be .txt .csv or .xlsx. Example file could be downloaded by clicking the **Example** button.



Click the **Submit** button to perform **SPPM** analysis.

Tip! Users should use only one way (A or B) to submit, otherwise Dr *AFC* will return an error warning.



3) **SPPM** analysis result

SPPM could automatically perform repositioning prediction and return a result page. The prediction result will be displayed in a seven-column table as following:

NUMBER: compound number.

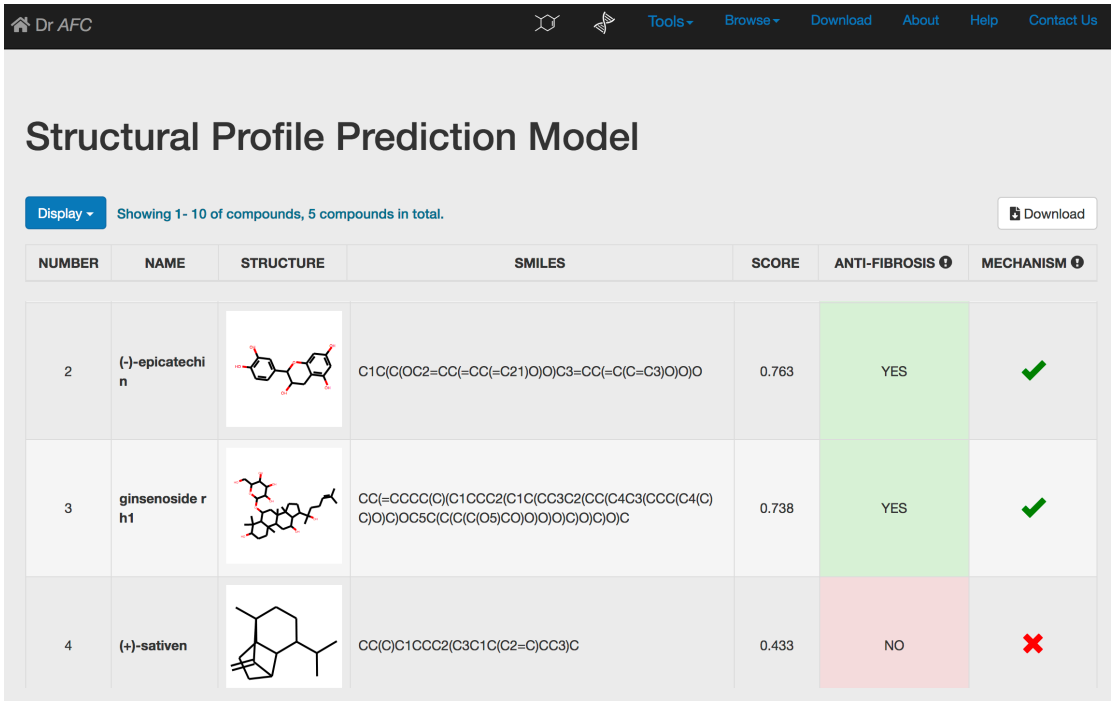
NAME: compound name.

STRUCTURE: the 2D chemical structure generated by SMILES string. Users could click the picture to visualize the structure on a new page.

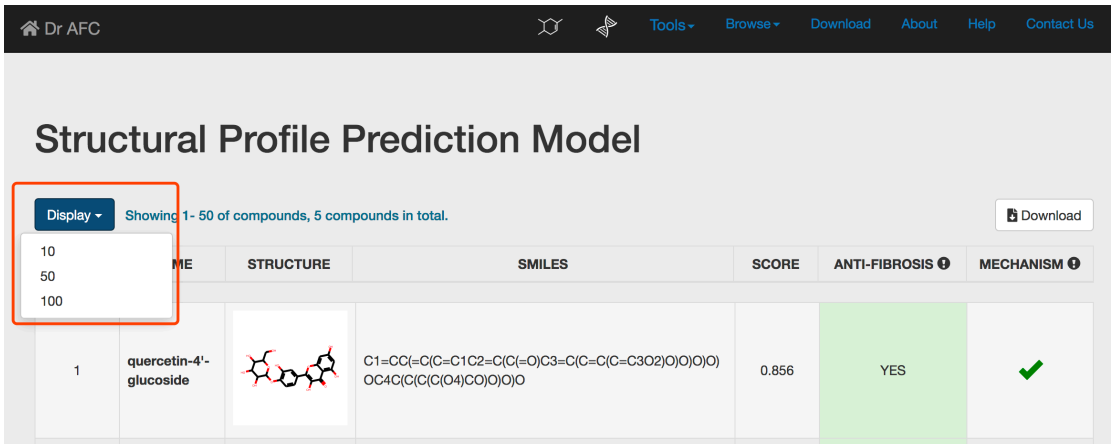
SCORE: anti-fibrosis and repositioning score(S) calculated by **SPPM**, ranging from 0 to 1. Higher score indicates stronger anti-fibrosis characteristic and repositioning potential.

ANTI-FIBROSIS: the anti-fibrosis status predicted by SPPM. Compounds with $S > 0.5$ would be defined as anti-fibrosis and labeled "YES". Otherwise, compounds would be labeled as "NO".

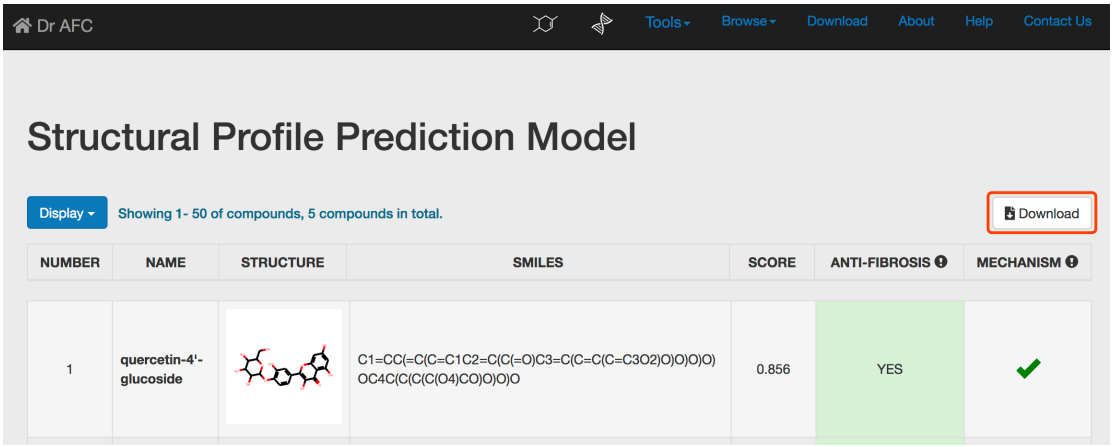
MECHANISM: drug repositioning mechanism analysis. See section 4 for more information.



Users can display first 10, 50 or 100 compounds through setting the **Display** drop-down list.



Click the **Download** button to download the entire prediction result table. The downloaded file is a tab separated text file.

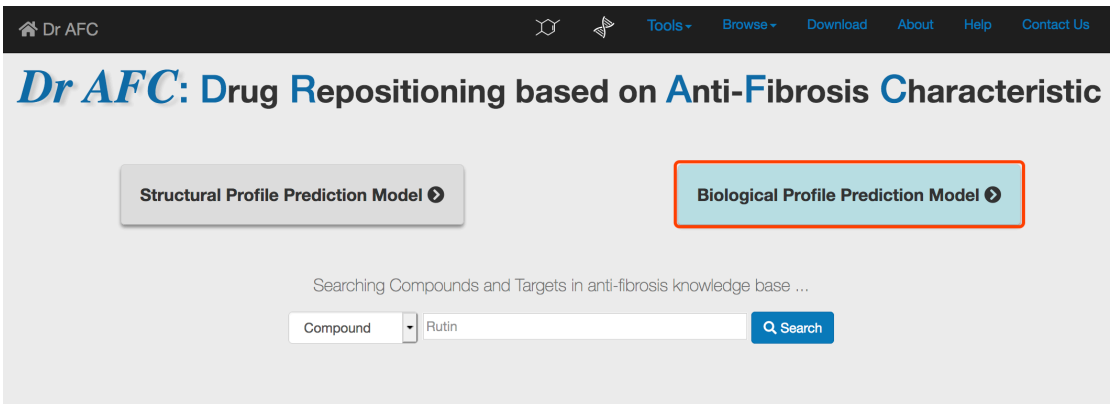


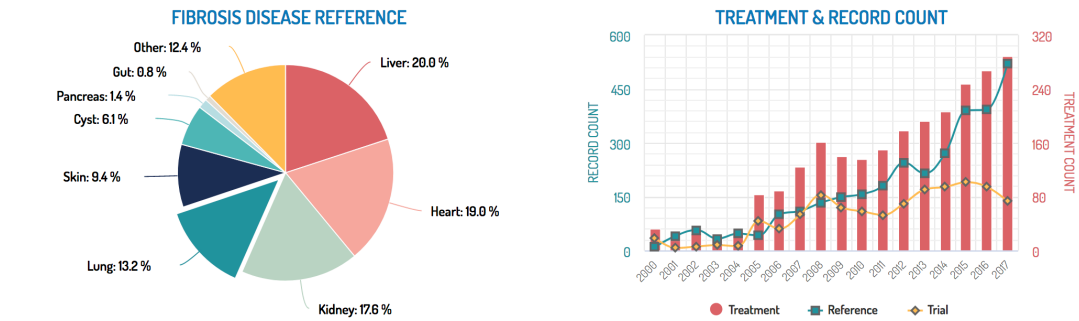
3. Drug Repositioning based on Biological Profile Prediction Model(BPPM)

If the study object of interest does not have a single SMILES string or direct structural information, such as a combination of drugs, BPPM of Dr *AFC* could be performed to predict their repositioning potential. **BPPM** could calculate anti-fibrosis and repositioning score(S) from biological profiles. The model was also constructed based on gradient boosting method and the optimal feature set used for modelling was selected by IFE algorithm. The compound-induced expression profiles could be submitted to the **BPPM** and Dr *AFC* will return repositioning results.

1) Enter the **BPPM** page

Similar to **SPPM**, click the **Biological Profile Prediction Model** to enter the **BPPM** submission page.



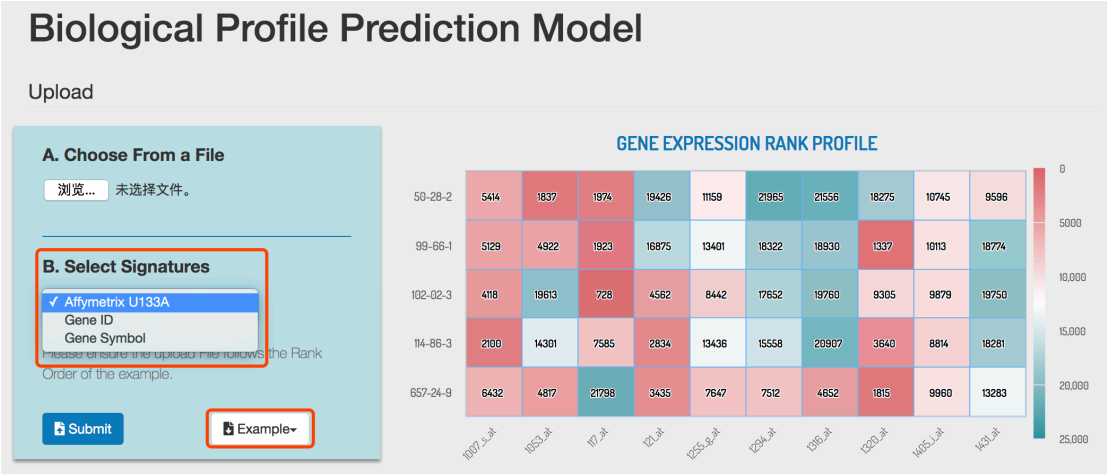


2) Submit biological profiles

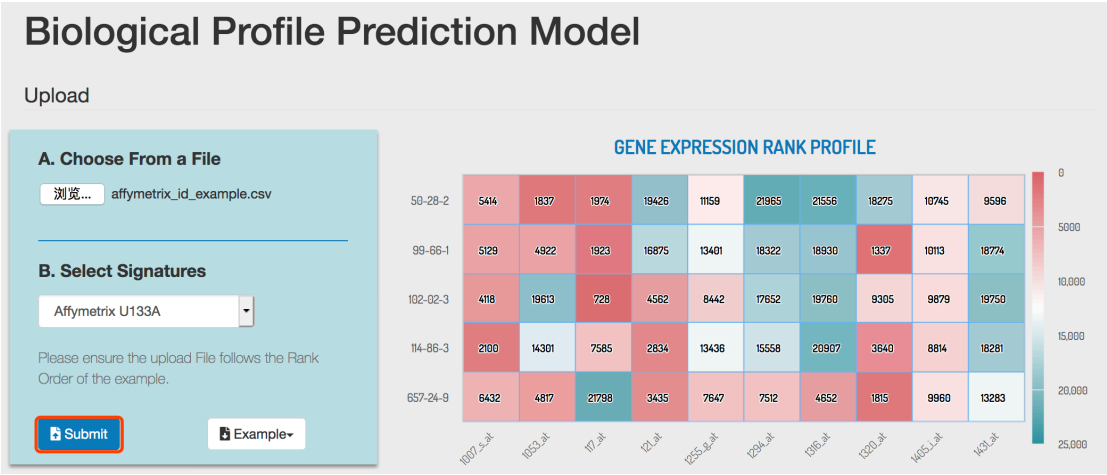
BPPM only accepts files containing expression profiles. The file should contain compound-induced

gene expressions with compound name as row name and gene name/probe ID as column name. Before submission, signature type should be specified as Affymetrix U133A ID, Gene ID or Gene symbol. Columns should be separated by Tab, comma or space character. The file format could be .txt .csv or .xlsx. Example file could be downloaded by clicking the **Example** button.

Tip! The order of signature by column in the uploaded file should match the order in the example.



Click the **Submit** button to perform **BPPM** analysis.



3) **BPPM** analysis result

BPPM could automatically perform repositioning prediction and return a result page. The prediction result will be displayed in a five-column table as following:

NUMBER: compound number.

NAME: compound name.

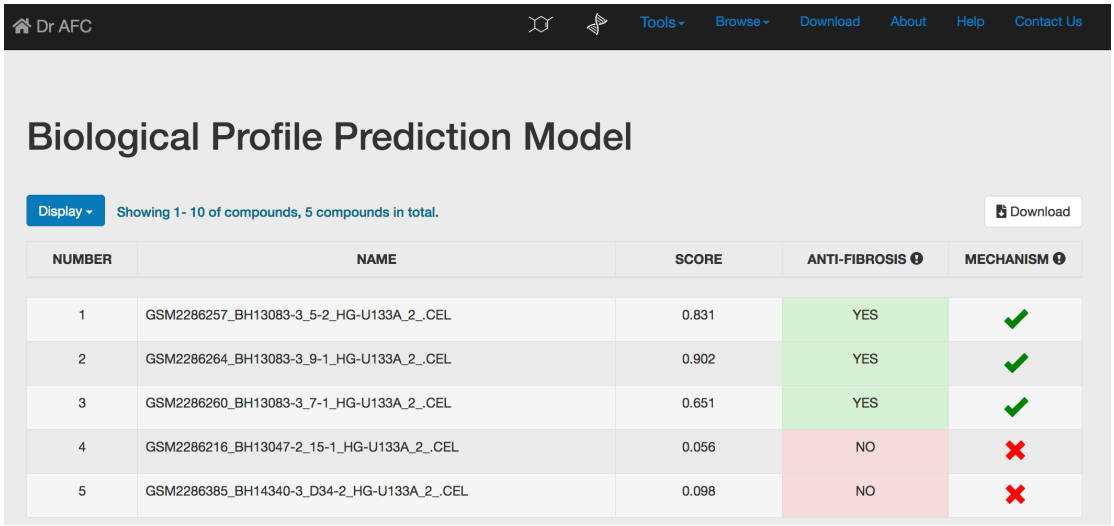
SCORE: anti-fibrosis and repositioning score(S) calculated by **BPPM**, ranging from 0 to 1. Higher score indicates stronger anti-fibrosis characteristic and repositioning potential.

ANTI-FIBROSIS: the anti-fibrosis status predicted by **BPPM**. Compounds with $S > 0.5$ would be defined as anti-fibrosis and potential repositioning compounds labeled as "YES". Otherwise, compounds would be labeled as "NO".

MECHANISM: drug repositioning mechanism analysis. See section 4 for more information.

Similar to the **SPPM** result page, **BPPM** result table can display first 10, 50 or 100 compounds

through setting the **Display** drop-down list. Users could click the **Download** button to download the entire prediction result table. The downloaded file is a tab separated text file. Please see section 2 for reference.



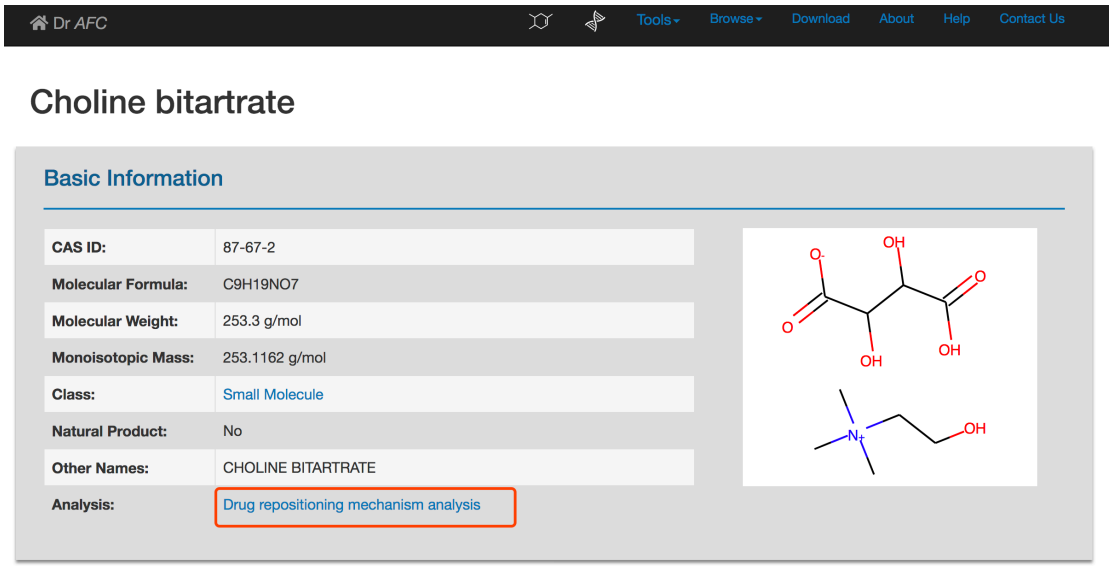
4. Drug Repositioning Mechanism Analysis

The **Drug Repositioning Mechanism Analysis** of Dr AFC could construct mechanism networks based on compound-target-disease corresponding information in the **Anti-fibrosis Knowledge Base**. Compounds that may interact with the same targets and diseases are predicted by calculating Tanimoto similarity on chemical structural fingerprints or calculating Spearman's rank correlation coefficient on biological profiles. Targets and disease information of compounds are extracted from the **Anti-fibrosis Knowledge Base** to explore the anti-fibrosis mechanism of compounds. The **Drug Repositioning Mechanism Analysis** displays potential mechanisms among compounds in compound-target-disease network to help discover feasible drug repositioning solutions.

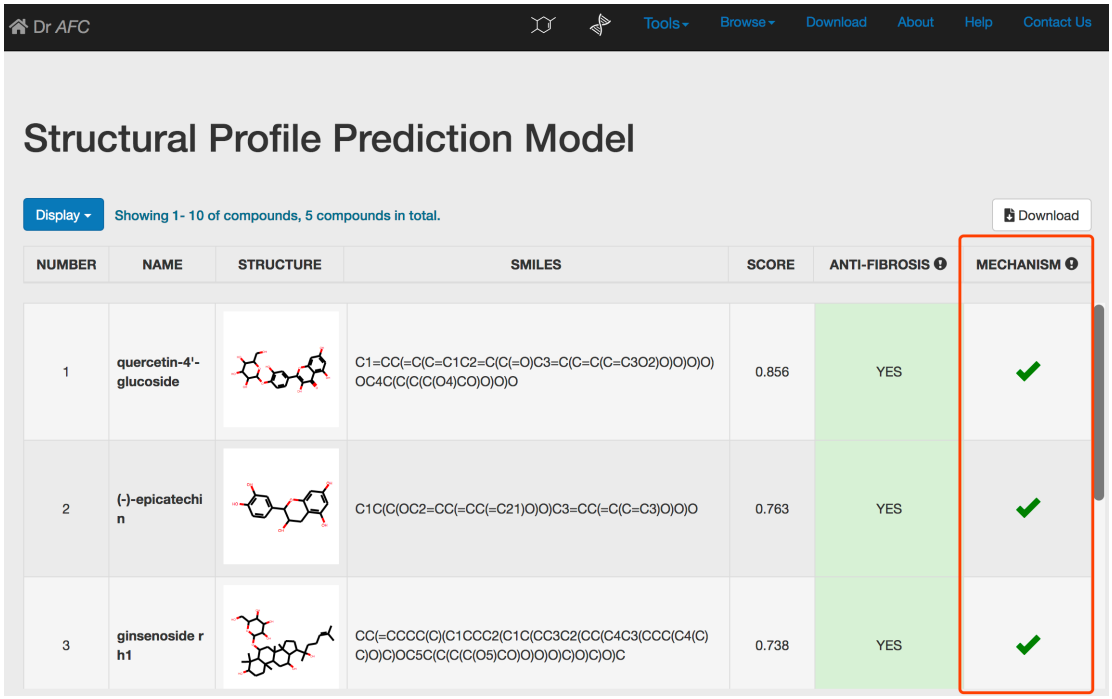
1) Enter the **Drug Repositioning Mechanism Analysis** page

The **Drug Repositioning Mechanism Analysis** could be accessed via **Compound** page or **SPPM/BPPM** result pages.

A. Click the **Drug repositioning mechanism analysis** to enter the **Drug Repositioning Mechanism Analysis** page from compound page.



B. Click the ✔ button to enter the **Drug Repositioning Mechanism Analysis** page from **SPPM/BPPM** result pages.



2) Display Repositioning Network

In the **Drug Repositioning Mechanism Analysis** page, repositioning network is displayed on the left.

The network pictures the potential repositioning mechanism of a query compounds by connecting it with various relevant compounds, targets and diseases.

In the network, each node represents a compound, target or disease. The node size represents the weight, reflecting confidence of the relevance. For example, a larger Blue diamond node represent compound more similar to the query compound. Edges stand for the interactions between

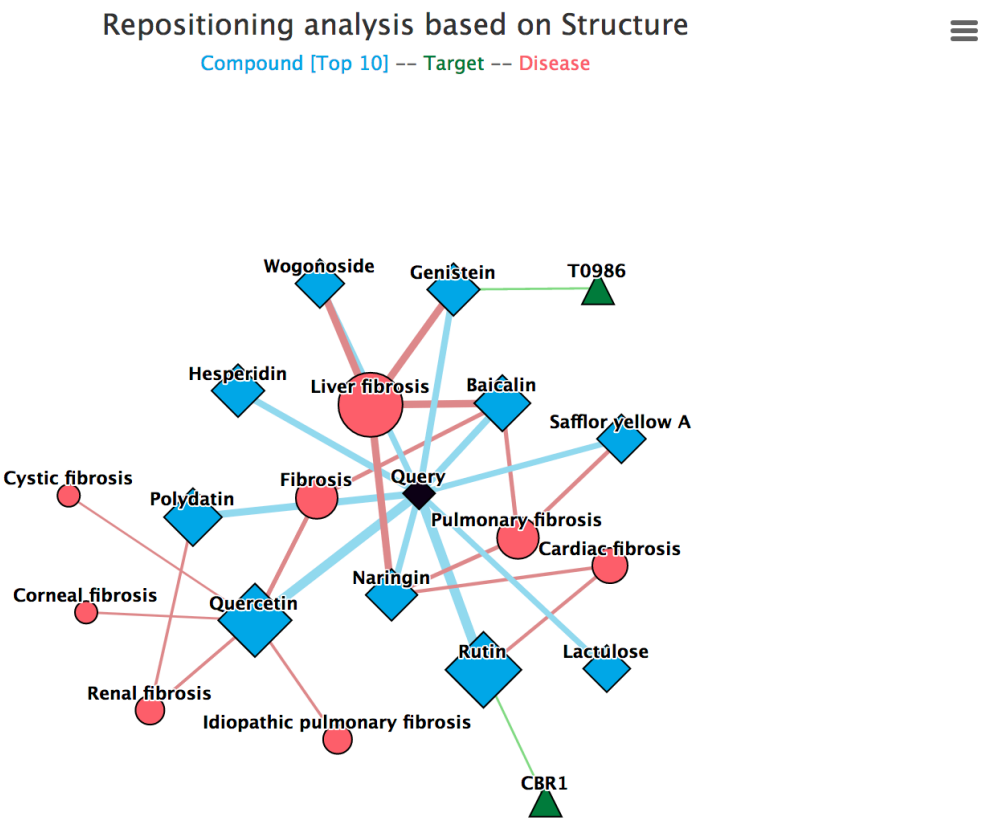
compound-compound, compound-target and compound-disease.

Black diamond: the query compound in **SPPM/BPPM** result page.

Blue diamond: compounds in the **Anti-fibrosis Knowledge Base** that are similar to the query compound according to Tanimoto similarity on chemical structural fingerprints or Spearman's rank correlation coefficient based on biological profiles.

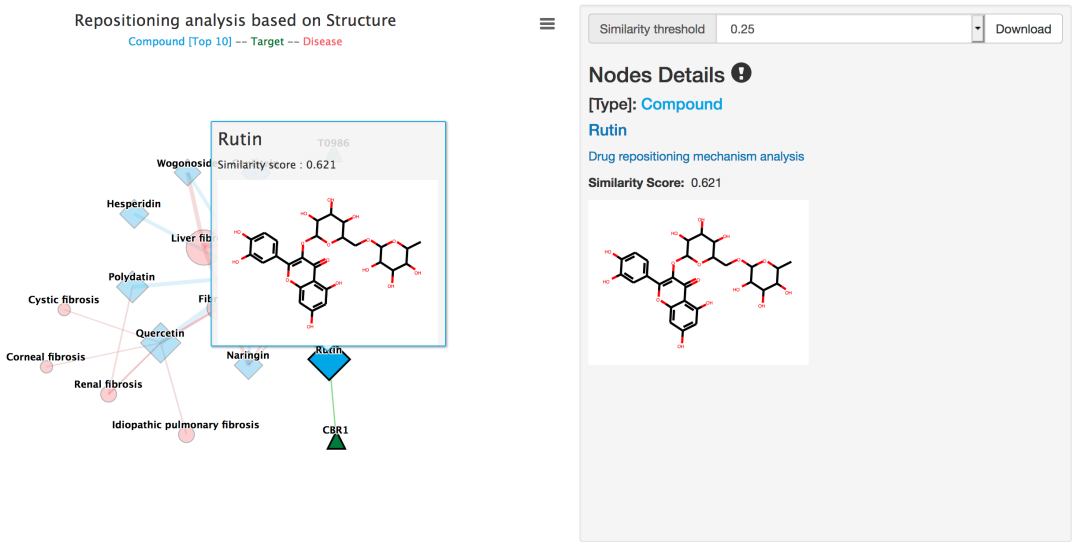
Green triangle: targets of compounds in the network.

Red round: fibrotic diseases related to compounds in the network.

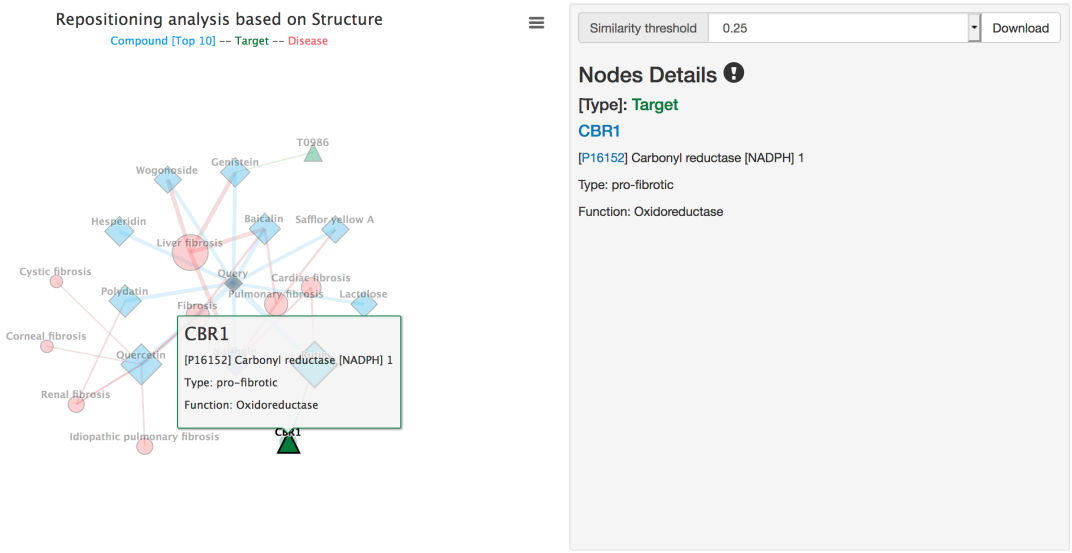


When users click the nodes, the detailed information will be displayed.

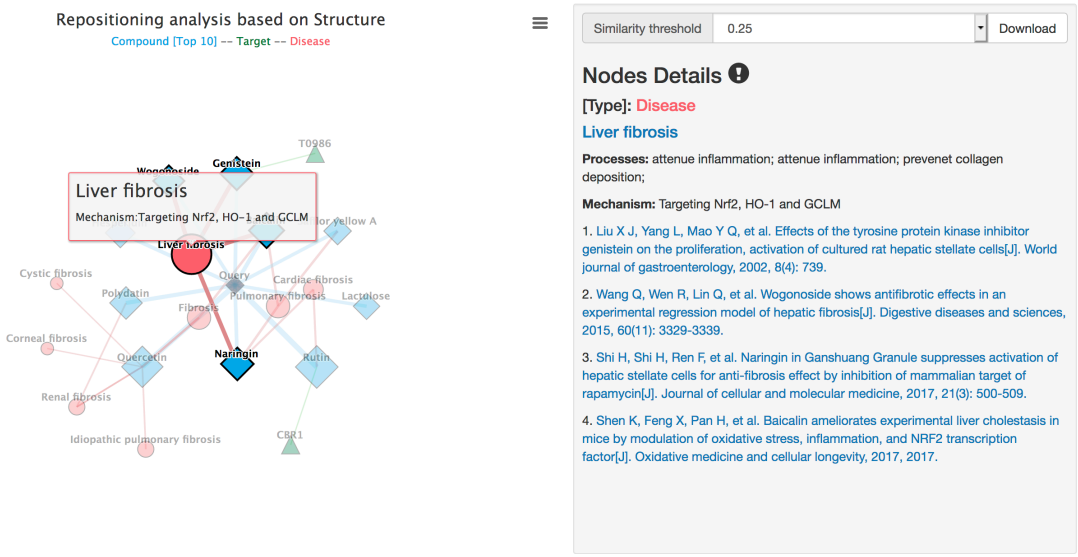
Details of compounds include node type, compound name linked to the **Compound** page, compound similarity score and the 2D chemical structure.



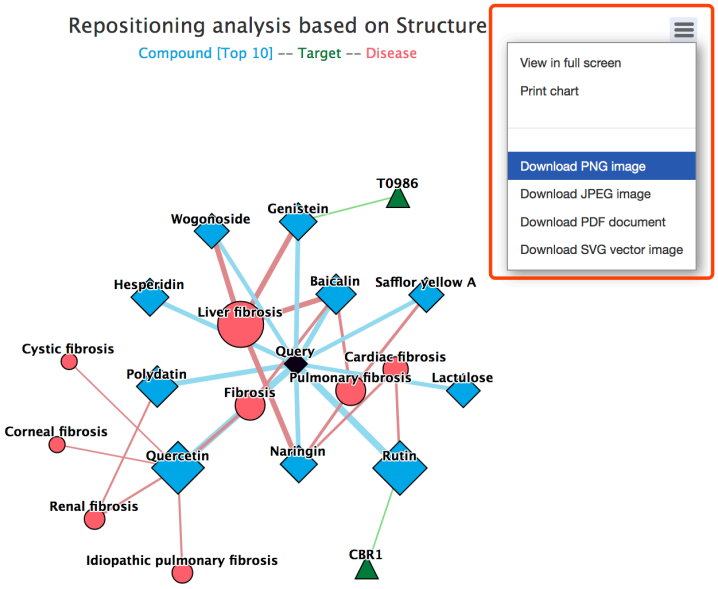
Details of targets include node type, UniProt ID, target name linked to the **Target** page, target type and target function.



Details of diseases include node type, disease linked to the PubMed MeSH, the anti-fibrosis mechanism and references of associated compounds.



Users can click the ☰ button to display the repositioning network in full screen view, to print or download the network. The network chart could be downloaded in .png, .jpeg, .pdf, or .svg format.



3) Network Details and Threshold Setting.

In the **Drug Repositioning Mechanism Analysis** page, network node details and threshold settings are displayed on the right.

The threshold is the minimum similarity score between the query compound and compounds from the **Anti-fibrosis Knowledge Base**. The threshold could be set to 0.25, 0.5, 0.75 or 1.

Click the **Download** button to download all the data of repositioning network.

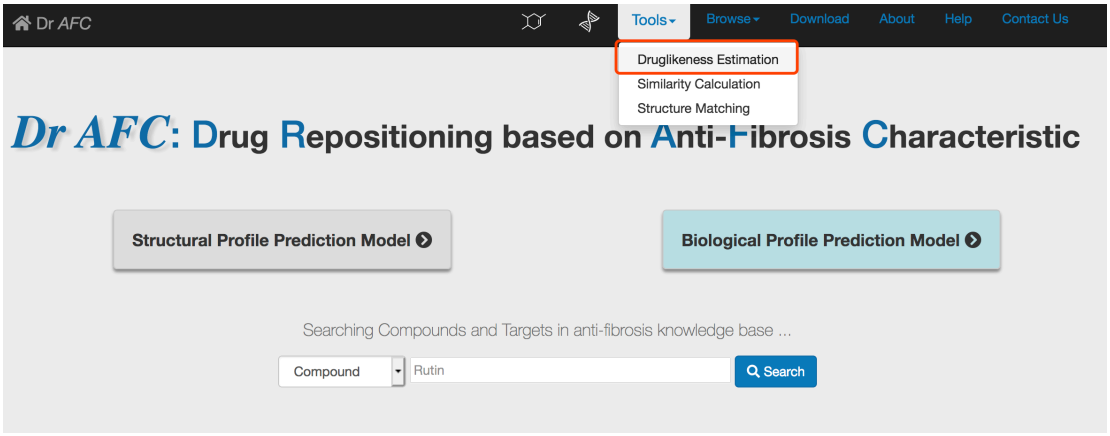
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	Reference_ID	PubMed_ID	Compound_	CAS_ID	Compound_	Target_ID	Uniprot_ID	Target_Nam	Model	Disease	Process1	Process2	Process3	Mechanism	Citation	year	Similarity_score
2	R0022	28826911	D0005	153-18-4	Rutin	T0487	P16152	Carbonyl re	mice	Cardiac fibrosis			prevenet co	Targeting Al	Huang R, Sh	2017	0.62121212
3	R0527	27286825	D0016	117-39-5	Quercetin				vitro	Cystic fibros	attenue inflammation			Targeting A	Malcomson	2016	0.59615385
4	R0047	28775044	D0016	117-39-5	Quercetin				vitro	Idiopathic pulmonary fib		cells apopto	prevenet co	collagen depos	Lehmann M	2017	0.59615385
5	R2831	19474275	D0016	117-39-5	Quercetin				vitro	Fibrosis			prevenet co	collagen depos	Hu, Qin, et a	2009	0.59615385
6	R0872	26151815	D0016	117-39-5	Quercetin				vitro,rat	Renal fibrosis		EMT	prevenet co	Targeting m	Lu Q, Ji X J,	2015	0.59615385
7	R0139	28549404	D0016	117-39-5	Quercetin				vitro,mice	Fibrosis		fibroblasts g	prevenet co	collagen depos	Doersch K M	2017	0.59615385
8	R0863	26173740	D0016	117-39-5	Quercetin				vitro	Corneal fibrosis					McKay T B, S	2015	0.59615385
9	R0611	27052477	D0016	117-39-5	Quercetin				vitro,mice	Renal fibrosi	attenue infla	fibroblasts a	prevenet co	Targeting M	Ren J, Li J, Li	2016	0.59615385
10	R1151	25192797	D0249	27208-80-6	Polydatin				vitro,rat	Renal fibrosis			prevenet co	Targeting Si	Huang K, Ch	2015	0.43548387
11	R0428	27658704	D0017	21967-41-9	Baicalin				mice	Pulmonary fibrosis			prevenet co	Targeting A	Huang X, He	2016	0.41791045
12	R0052	28757911	D0017	21967-41-9	Baicalin				vitro,mice	Liver fibrosis	attenue inflammation		prevenet co	Targeting N	Shen K, Fen	2017	0.41791045
13	R2832	19474275	D0017	21967-41-9	Baicalin				vitro	Fibrosis			prevenet co	collagen depos	Hu, Qin, et a	2009	0.41791045
14	R2727	12174389	D0485	446-72-0	Genistein	T0986	PF07714	Protein tyro	vitro,rat	Liver fibrosis		HSCs proliferation			Liu X J, Yang	2002	0.37931034
15	R0423	27687505	D0114	10236-47-2	Naringin				vitro,mice	Liver fibrosis		HSC activation		Targeting m	Shi H, Shi H,	2017	0.37179487
16	R2759	27174133	D0114	10236-47-2	Naringin				rat	Cardiac fibrosis			prevenet co	Targeting T(	Adil, Moham	2016	0.37179487

5. Druglikeness Estimation

The **Druglikeness Estimation** of Dr *AFC* could calculate the *quantitative estimation of drug-likeness*(QED) for compound, i.e., the druglikeness, based on structural profile[4]. The compound druglikeness reflects the underlying distribution of molecular properties and could serve for the druggability assessment. SMILES strings of compounds could be submitted and the **Druglikeness Estimation** of Dr *AFC* will return estimation results.

1) Enter the **Druglikeness Estimation** page

Click the **Tools | Druglikeness Estimation** to enter the **Druglikeness Estimation** submission page.

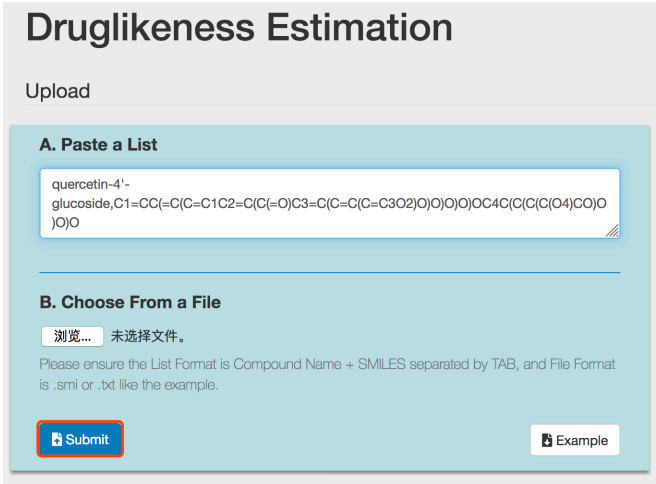


2) Submit compound structures

Like other functionalities of Dr *AFC*, **Druglikeness Estimation** accepts compound structure in two ways, and users can choose either way to submit. The example file of **Druglikeness Estimation** could also be downloaded by clicking the **Example** button. Please see section 2 for reference.

Click the **Submit** button to perform druglikeness estimation.

Tip! Users should use only one way to submit, otherwise Dr *AFC* will return an error warning.



3) **Druglikeness Estimation** result

Druglikeness Estimation could automatically perform druglikeness estimation and return a result page. The estimation result will be displayed in a ten-column table.

NAME: compound name.

MW: compound molecular weight.

ALOGP: the octanol-water partition coefficient of compound.

HBA: the number of hydrogen bond acceptors of compound.

HBD: the number of hydrogen bond donors of compound.

PSA: the molecular polar surface area of compound.

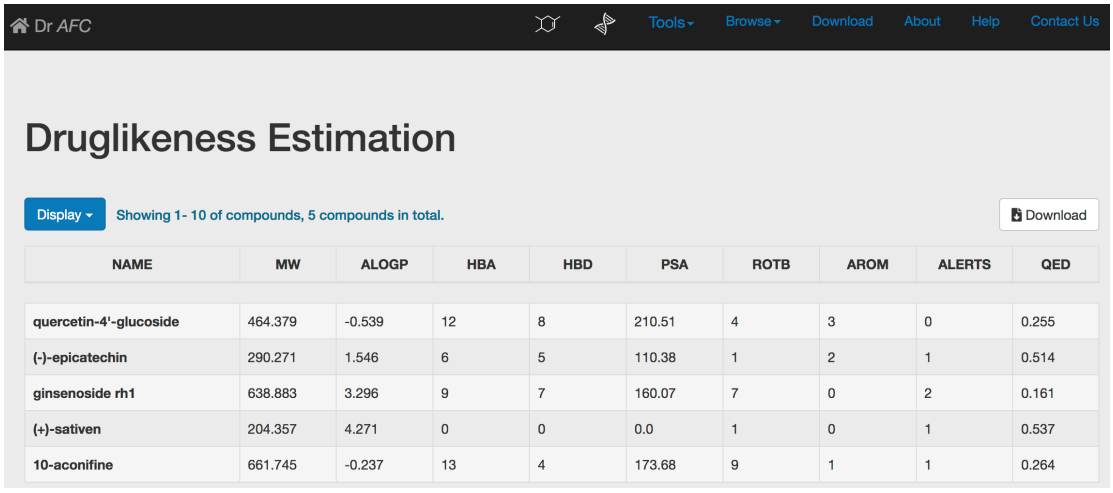
ROTB: the number of rotatable bonds of compound.

AROM: the number of aromatic rings of compound.

ALERTS: the number of matches for each compound captured.

QED: the druglikeness score, ranging from 0 to 1. Higher score indicates higher druggability.

Same as the **SPPM** result page, **Druglikeness Estimation** result table could display first 10, 50 or 100 compounds through setting the **Display** drop-down list. Users could click the **Download** button to download the entire prediction result. The downloaded file is a text file separated by Tab. Columns of the downloaded file will be the same as the displayed table. Please see section 2.



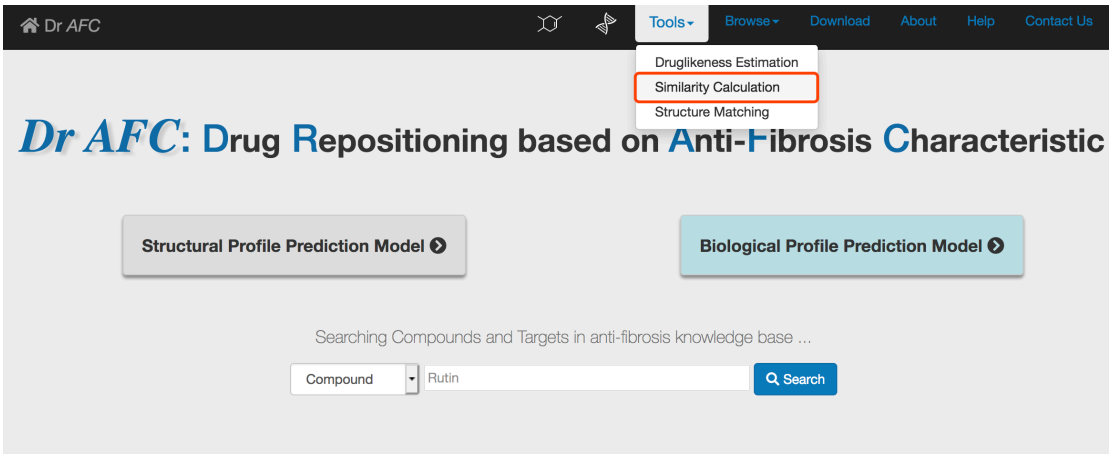
NAME	MW	ALOGP	HBA	HBD	PSA	ROTB	AROM	ALERTS	QED
quercetin-4'-glucoside	464.379	-0.539	12	8	210.51	4	3	0	0.255
(-)-epicatechin	290.271	1.546	6	5	110.38	1	2	1	0.514
ginsenoside rh1	638.883	3.296	9	7	160.07	7	0	2	0.161
(+)-sativen	204.357	4.271	0	0	0.0	1	0	1	0.537
10-aconifine	661.745	-0.237	13	4	173.68	9	1	1	0.264

6. Similarity Calculation

The **Similarity Calculation** of Dr *AFC* could calculate the Tanimoto similarity between submitted compounds and anti-fibrosis compounds in **Anti-fibrosis Knowledge Base**. The molecular similarity is calculated through R-based package in RDkit[5]. SMILES strings of compounds could be uploaded and the **Similarity Calculation** of Dr *AFC* will return calculation results.

1) Enter the **Similarity Calculation** page

Click the **Tools** | **Similarity Calculation** to enter the **Similarity Calculation** submission page.



2) Submit compound structures

Similarity Calculation accepts both single compound and multiple compounds and return different result pages.

In single compound submission, enter or paste the SMILES string of compound and click the **Submit** button to perform similarity calculation.

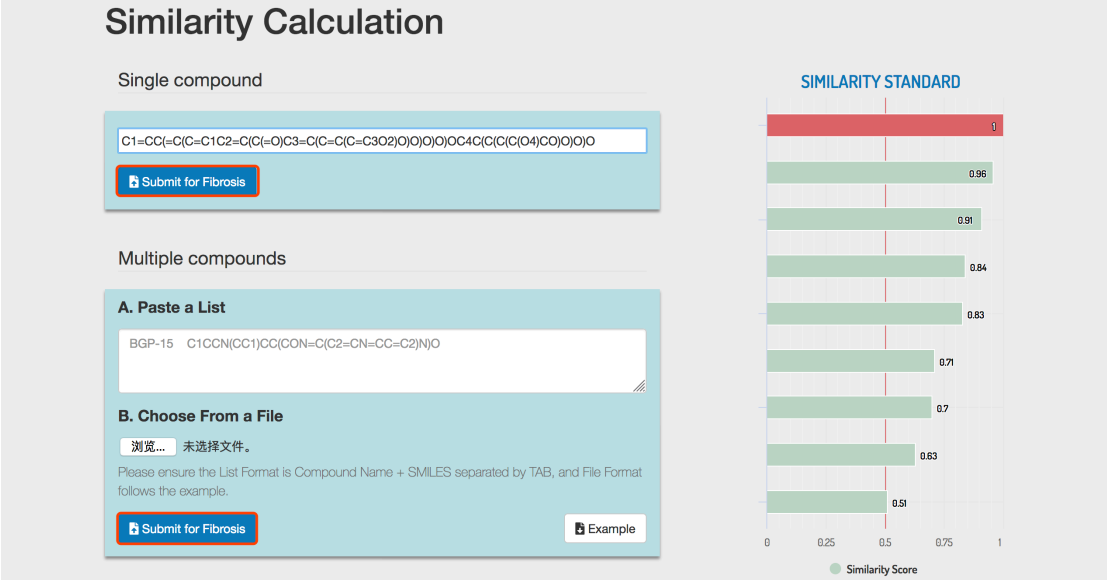
e.g.

C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)OC4C(C(C(C(O4)CO)O)O)O

In multiple compounds submission, **Similarity Calculation** accepts compound structures in two ways, and users can choose either way to submit. The example file of **Similarity Calculation** could also be downloaded by clicking the **Example** button. Please see section 2.

Click the **Submit** button to perform similarity calculation.

Tip! Users should use only one way to submit, otherwise Dr *AFC* will return an error warning.



3) **Similarity Calculation** result

If single compound is submitted**, Similarity Calculation** could automatically perform similarity calculation and return a result page. The calculation result will be displayed in a five-column table.

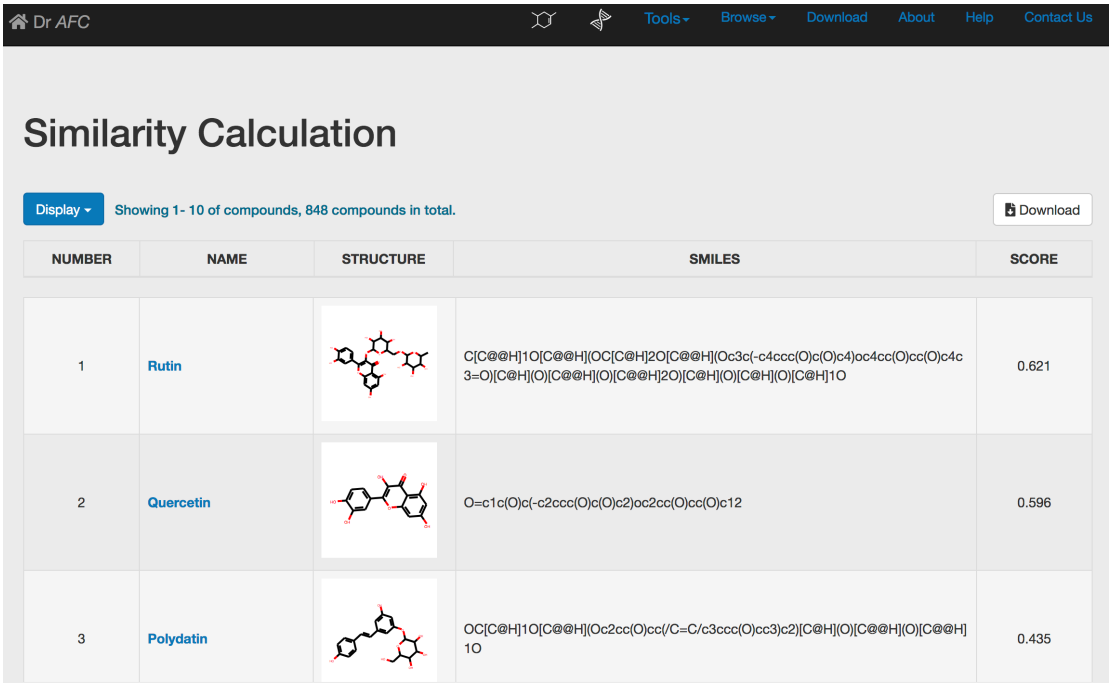
NUMBER: compound order ranked by similarity score.

NAME: retrieved compound name from the **Anti-fibrosis Knowledge Base**.

STRUCTURE: the 2D chemical structure generated by SMILES string. Users could click the picture to zoom in the chemical structure in a new page.

SMILES: the SMILES string of compound.

SCORE: calculated Tanimoto similarity score, ranging from 0 to 1. Higher score indicates higher similarity.



If multiple compounds are submitted, **Similarity Calculation** would return a different result page. The calculation result will be displayed in a twelve-column table.

NAME: compound name.

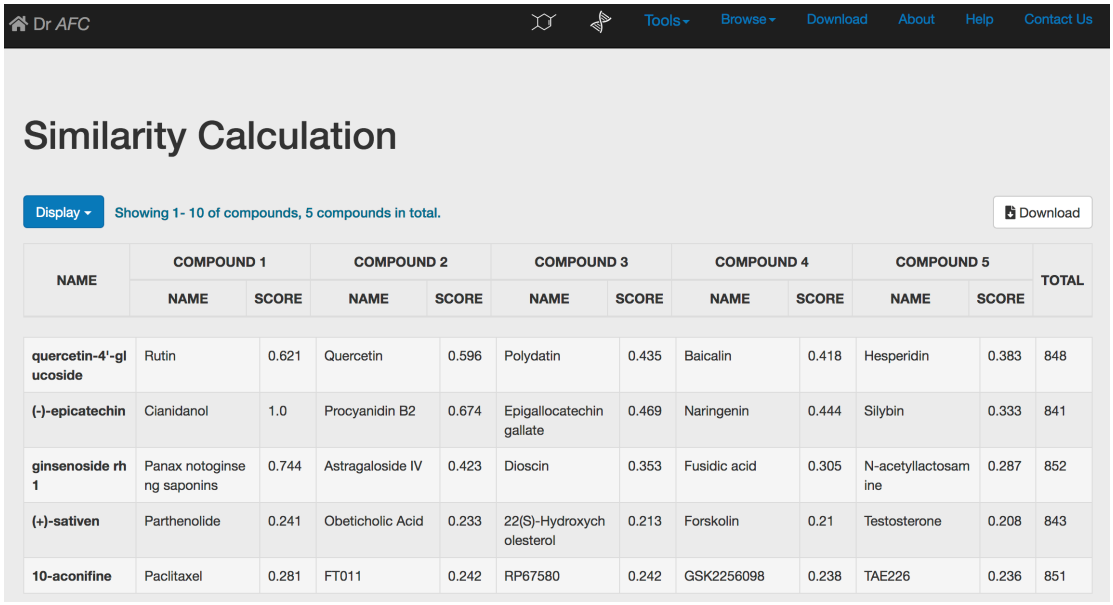
COMPOUND 1(NAME): the first compound name ranked by similarity score in the **Anti-fibrosis Knowledge Base**.

COMPOUND 1(SCORE): the similarity score of top ranked compound.

(Like COMPOUND 1, COMOUND 2-5 refer to the subsequent compounds and their scores)

TOTAL: the total number of retrieved compounds from the **Anti-fibrosis Knowledge Base**.

As before, two different **Similarity Calculation** result tables could display first 10, 50 or 100 compounds through setting the **Display** drop-down list. Users could click the **Download** button to download the entire calculation result. The downloaded file is a text file separated by Tab. The file columns are the same as the displayed table. Please see section 2.



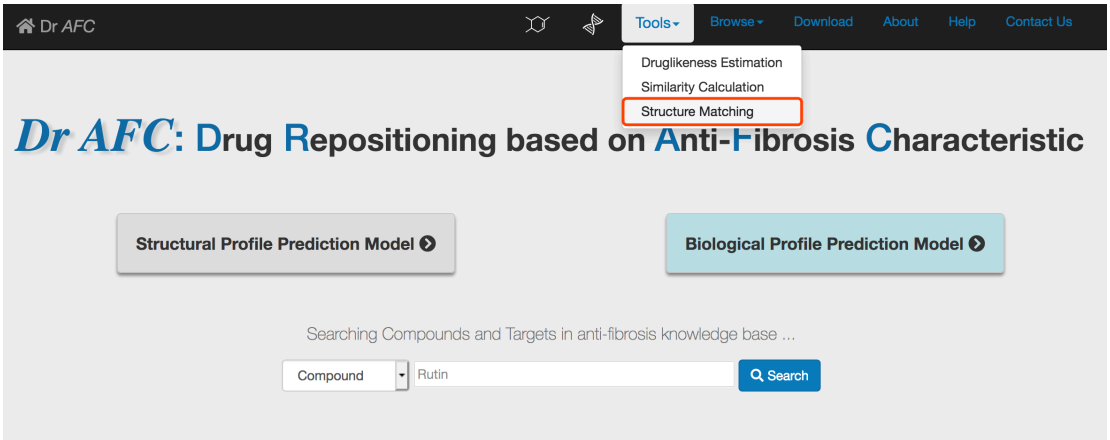
NAME	COMPOUND 1		COMPOUND 2		COMPOUND 3		COMPOUND 4		COMPOUND 5		TOTAL
	NAME	SCORE	NAME	SCORE	NAME	SCORE	NAME	SCORE	NAME	SCORE	
quercetin-4'-glucoside	Rutin	0.621	Quercetin	0.596	Polydatin	0.435	Baicalin	0.418	Hesperidin	0.383	848
(-)-epicatechin	Cianidanol	1.0	Procyanidin B2	0.674	Epigallocatechin gallate	0.469	Naringenin	0.444	Silybin	0.333	841
ginsenoside rh1	Panax notoginseng saponins	0.744	Astragaloside IV	0.423	Dioscin	0.353	Fusidic acid	0.305	N-acetyllactosamine	0.287	852
(+)-sativen	Parthenolide	0.241	Obeticholic Acid	0.233	22(S)-Hydroxycholesterol	0.213	Forskolin	0.21	Testosterone	0.208	843
10-aconifine	Paclitaxel	0.281	FT011	0.242	RP67580	0.242	GSK2256098	0.238	TAE226	0.236	851

7. Structure Matching

The **Structure Matching** of Dr *AFC* could look for compound from **Anti-fibrosis Knowledge Base** that match exactly the query compound, or match the query compound with its substructure. The matching is performed based on RDkit[5]. SMILES strings of compounds could be uploaded and the **Structure Matching** of Dr *AFC* will return matching results.

1) Enter the **Structure Matching** page

Click the **Tools | Structure Matching** to enter the **Structure Matching** submission page.



2) Submit compound structures

Structure Matching accepts both single compound and multiple compounds. Furthermore, **Structure Matching** could perform exact structure matching and substructure matching.

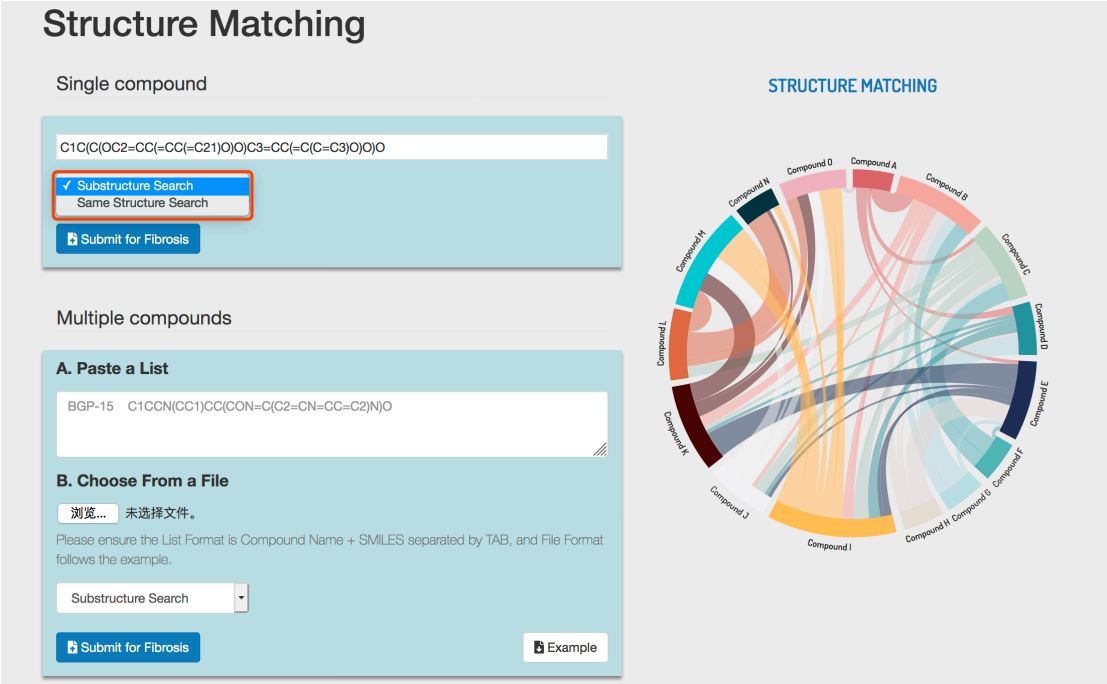
In single compound submission, enter or paste the SMILES string of compound and click the **Submit** button to perform similarity calculation.

e.g. *C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O*

In multiple compounds submission, **Structure Matching** accepts compound structures in two ways, and users can choose either way to submit. The example file of **Structure Matching** could also be downloaded by clicking the **Example** button. Please see section 2.

Select **Substructure Search** or **Same Structure Search**. Click the **Submit** button to perform structure matching.

Tip! Users should use only one way to submit, otherwise Dr *AFC* will return an error warning.



3) **Structure Matching** result

If single compound is submitted**, Structure Matching** could automatically perform similarity

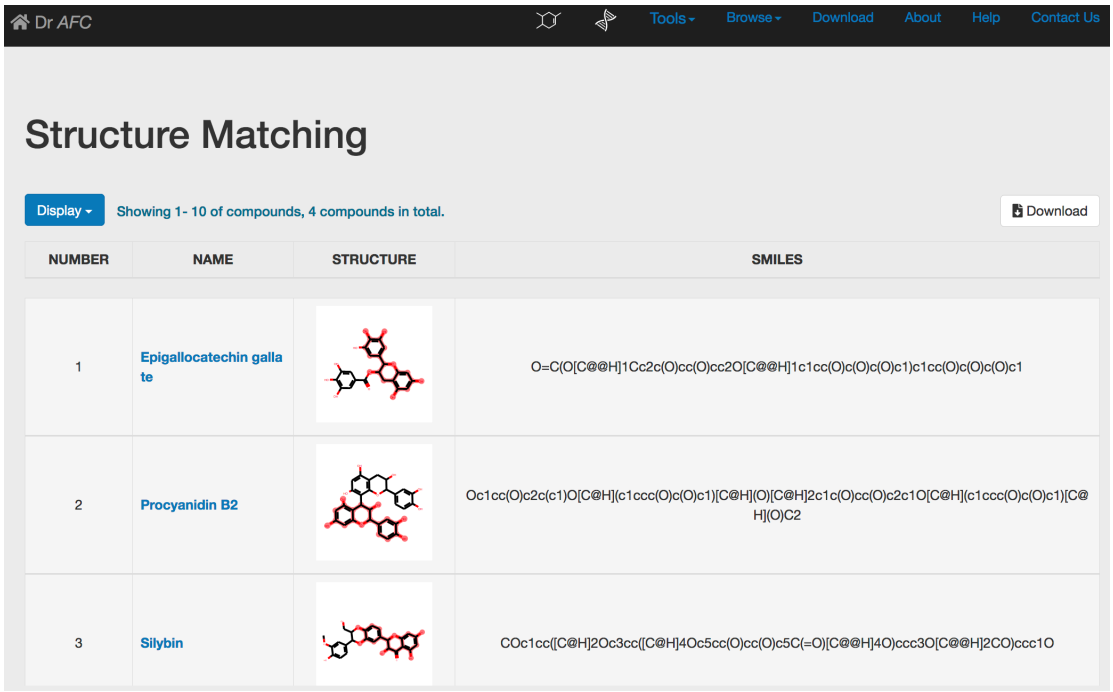
calculation and return a result page. The calculation result will be displayed in a four-column table.

NUMBER: compound ranked by similarity score.

NAME: retrieved compound name from the **Anti-fibrosis Knowledge Base**.

STRUCTURE: the 2D chemical structure generated by SMILES string. In **Substructure Search**, the submitted structures are highlighted in red. Users could click the picture to zoom in the chemical structure in a new page.

SMILES: the SMILES string of compound.



If multiple compounds are submitted, **Structure Matching** would return a different result page. The calculation result will be displayed in a five-column table.

NAME: compound name.

COMPOUND 1: the first compound name ranked by similarity score in the **Anti-fibrosis Knowledge Base**.

(As COMPOUND 1, COMOUND 2-5 refer to the corresponding ranked compounds)

TOTAL: the total number of retrieved compounds in **Anti-fibrosis Knowledge Base**.

As before, two different **Structure Matching** result tables could display first 10, 50 or 100 compounds through setting the **Display** drop-down list. Users could click the **Download** button to download the entire matching result. The downloaded file is a text file separated by Tab. The downloaded file columns are the same as the displayed table. Please see section 2.

References

1. Davis, A.P., et al., *The Comparative Toxicogenomics Database: update 2019.* Nucleic Acids Res, 2019. **47**(D1): p. D948-D954.
2. Zarin, D.A., et al., *10-Year Update on Study Results Submitted to ClinicalTrials.gov.* N Engl J Med, 2019. **381**(20): p. 1966-1974.
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4. Bickerton, G.R., et al., *Quantifying the chemical beauty of drugs.* Nat Chem, 2012. **4**(2): p. 90-8.
5. Landrum, G., *RDKit: Open-source cheminformatics.* 2006.