



User's Manual

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MANORAA user's Manual

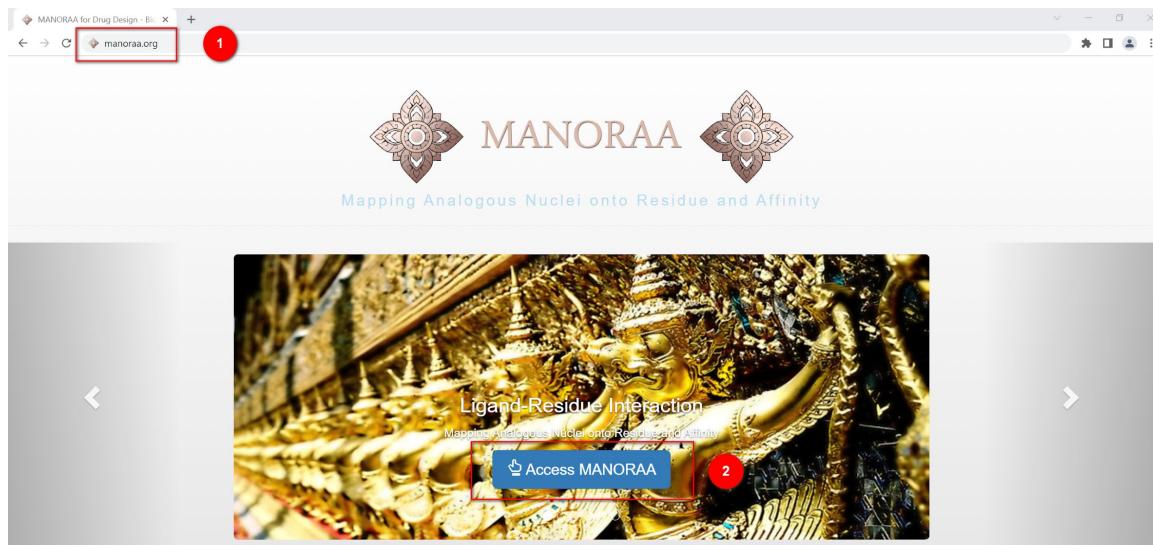
MANORAA is a website to assist structure-based drug design. The webservice is developed by the Integrative Computational BioScience (ICBS) Center, Mahidol University. Its database consisted of 116,864 PDB structures and 22,506 ligands. The users can download the output in the form of CSV file. There is also support for API and 3D visualization of protein structure from this webservice.

1. MANORAA webserver access

MANORAA system is freely accessible without user's registration. The users can access by entering <https://manoraa.org> at the web browser search panel.

(1) Open Google Chrome or Mozilla Firefox and type the URL <https://manoraa.org> on the URL panel

(2) After reaching the webservice, click on "Access MANORAA" to start the service.



2. Menu Bars to access functions

Copyright: Manoraa Project, ICBS Center, Mahidol University

On the MANORAA's website, there is this main searching panel as shown below.

The screenshot shows the MANORAA website interface. At the top, there is a navigation bar with five items: 'Browse by Drugs', 'Sample', 'Howto', 'About', and 'Powered by MANORAA'. The 'Powered by MANORAA' item is followed by a dropdown arrow. Below the navigation bar is a section titled 'Query Method'. This section contains input fields for 'e.g. KPCT_HUMAN' (labeled 2) and 'e.g. STU'. There are also radio buttons for 'SMILES' and 'PDB Ligand'. On the right side of the 'Query Method' section is a Marvin JS chemical editor interface, which includes a toolbar with various chemical structures and a legend for elements (H, C, N, O, S, F, P, Cl, Br, I). The Marvin JS logo and 'by Chemaxon' are also present.

The top panel (1) consists of 5 menu bars as follows.

- Browse by Drugs: The lists of access to DrugBank's items on WRITE
- Sample: An example of Staurosporine (STU), a workable test case across every function
- Howto: Video clips describing how to use MANORAA
- About: Published scientific papers about MANORAA
- Powered by MANORAA: Other servers that relates to drug design using MANORAA backend & algorithms

The second panel (2) allows desired chemical input to get start on using MANORAA

3. MANORAA Drug Browser

User can click on the menu “Browse by Drugs” to reach all the drug compounds in the system

The panel below is shown when clicking on Browse by Drugs

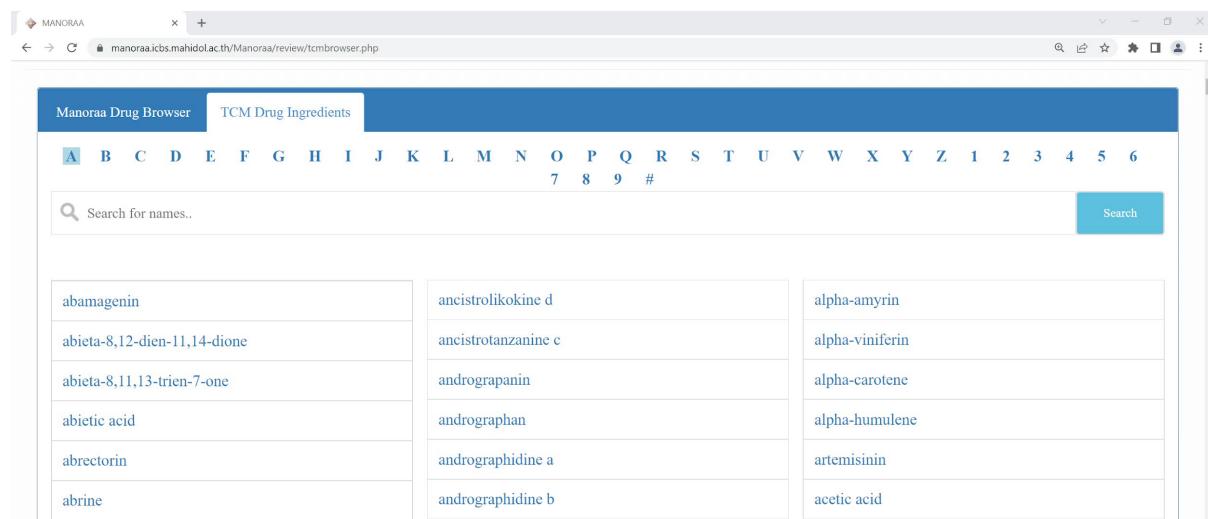
TCM Drug Ingredients	Code
Aminopterin	04J
Alprazolam	08H
Afatinib	0WM
AZD-5363	0XZ
Atorvastatin	117
Apabetalone	1K0
AL5424	AL2
AL5300	AL3
AL4623	AL4
AL6528	AL6
AL7099A	AL7
AL7089A	AL8

The components of the “Browse by Drugs” page are as follows

- (1) Drug Tabs – There are 2 tabs, the evidenced-based drug on “Drug Browser” and the Traditional Chinese Medicine (TCM) Drug Ingredients.
- (2) Alphabetical Index – Users can click on the letters to reach the initials of the drug names
- (3) Search Bar – The search panels with recommendations to the input alphabets
- (4) The list of output entries – The output of several drugs retrieved from the ligands/drug input query

Drug Browser Tabs

The drug browser tabs are divided into evidence-based drug browser and Traditional Chinese Medicine (TCM) drug ingredients. Examples below from TCM, are listed by alphabet A.



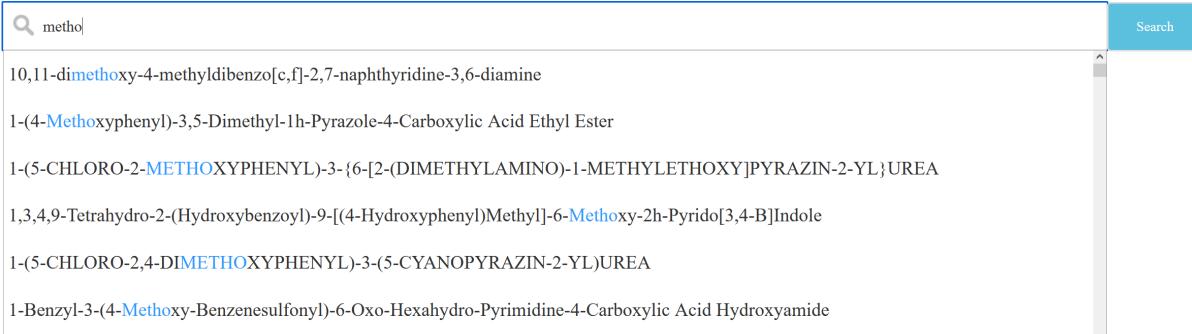
abamagenin
abiesta-8,12-dien-11,14-dione
abiesta-8,11,13-trien-7-one
abietic acid
abrectorin
abrine

ancistrolikokine d
ancistrotanzanine c
andrograpanin
andrographan
andrographidine a
andrographidine b

alpha-amyrin
alpha-viniferin
alpha-carotene
alpha-humulene
artemisinin
acetic acid

Search Bar

The search bar is used for guessing the input query. The users can either match similar words, or search the exact term and then click on search to find the drug name.

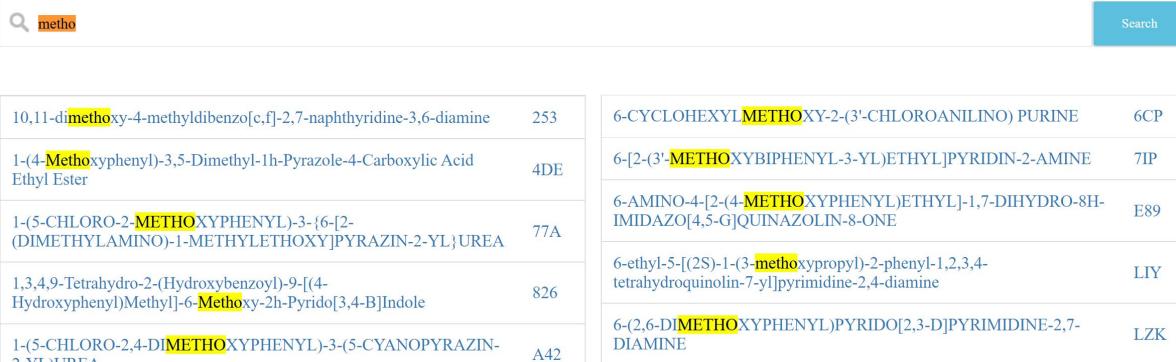


A screenshot of a search interface. The search bar at the top contains the text "metho". To the right of the search bar is a blue "Search" button. Below the search bar, a list of search results is displayed in a scrollable box. The results are as follows:

- 10,11-dimethoxy-4-methyldibenzo[c,f]-2,7-naphthyridine-3,6-diamine
- 1-(4-Methoxyphenyl)-3,5-Dimethyl-1h-Pyrazole-4-Carboxylic Acid Ethyl Ester
- 1-(5-CHLORO-2-METHOXYPHENYL)-3-{6-[2-(DIMETHYLAMINO)-1-METHYLETHOXY]PYRAZIN-2-YL}UREA
- 1,3,4,9-Tetrahydro-2-(Hydroxybenzoyl)-9-[(4-Hydroxyphenyl)Methyl]-6-Methoxy-2h-Pyrido[3,4-B]Indole
- 1-(5-CHLORO-2,4-DIMETHOXYPHENYL)-3-(5-CYANOPYRAZIN-2-YL)UREA
- 1-Benzyl-3-(4-Methoxy-Benzenesulfonyl)-6-Oxo-Hexahydro-Pyrimidine-4-Carboxylic Acid Hydroxyamide

The listed entry

This is the list of output entries to show all the drug names that matches with the input queries.



A screenshot of a search interface showing a list of drug names and their corresponding three-letter codes. The table is divided into two columns. The left column lists the drug names, and the right column lists the three-letter codes. The entries are as follows:

10,11-dimethoxy-4-methyldibenzo[c,f]-2,7-naphthyridine-3,6-diamine	253
1-(4-Methoxyphenyl)-3,5-Dimethyl-1h-Pyrazole-4-Carboxylic Acid Ethyl Ester	4DE
1-(5-CHLORO-2-METHOXYPHENYL)-3-{6-[2-(DIMETHYLAMINO)-1-METHYLETHOXY]PYRAZIN-2-YL}UREA	77A
1,3,4,9-Tetrahydro-2-(Hydroxybenzoyl)-9-[(4-Hydroxyphenyl)Methyl]-6-Methoxy-2h-Pyrido[3,4-B]Indole	826
1-(5-CHLORO-2,4-DIMETHOXYPHENYL)-3-(5-CYANOPYRAZIN-2-YL)UREA	A42
6-CYCLOHEXYL METHOXY-2-(3'-CHLOROANILINO) PURINE	6CP
6-[2-(3'-METHOXYBIPHENYL-3-YL)ETHYL]PYRIDIN-2-AMINE	7IP
6-AMINO-4-[2-(4-METHOXYPHENYL)ETHYL]-1,7-DIHYDRO-8H-IMIDAZO[4,5-G]QUINAZOLIN-8-ONE	E89
6-ethyl-5-[(2S)-1-(3-methoxypropyl)-2-phenyl-1,2,3,4-tetrahydroquinolin-7-yl]pyrimidine-2,4-diamine	LIY
6-(2,6-DIMETHOXYPHENYL)PYRIDO[2,3-D]PYRIMIDINE-2,7-DIAMINE	LZK

After clicking on the names, the output will be retrieved by matching the SMILES string with PDB's 3-letter codes. On the other hand, the three letter codes on the side are the exact matches of the compound name and also the quickest way to retrieve the tabulated output results.

Aminopterin

Aminopterin

Ligand structures in Complex with smiles:

Nc1nc2c(nc(CNc3ccc(cc3)C(=O)N[C@@H](CCC(=O)O)C(=O)O)cn2)c(N)n1

Please select ligand substructures and their interacting PDB chains

CHEMBL2104643

CHEMBL1413109

CHEMBL274619

CHEMBL376180

Filter by Categories

Uniprot ID

Pathway

UniProt Acc

PDB

Resolution(Å)

Chain

Affinity(µM)

Ligand Structure

04J
Select substructures:
Heteroatom:
 N N1 N3 N5 N8
 N10 NA2 NA4 O O1
 O2 OE1 OE2 All

 C C2 C4 C4A C6
 C7 C8A C9 C11 C12
 C13 C14 C15 C16 CA
 CB CD CG CT All

PDB Chains

04J

CSV + PDB

Uniprot & Variants	Pathways	Target Protein	PDB	Resolution(Å)	Chain	Affinity(µM)
P14207	hsa:2350	FOLR2_HUMAN	4KN1	2.3	<input checked="" type="checkbox"/> A	0.144

Showing 1 to 1 of 1 entries

Ligand Structure

MT1
Select substructures:
Heteroatom:
 D D1 N N1 N3
 N5 N8 N10 NA2 NA4
 O O1 O2 OE1 OE2
 All

PDB Chains

MT1

CSV + PDB

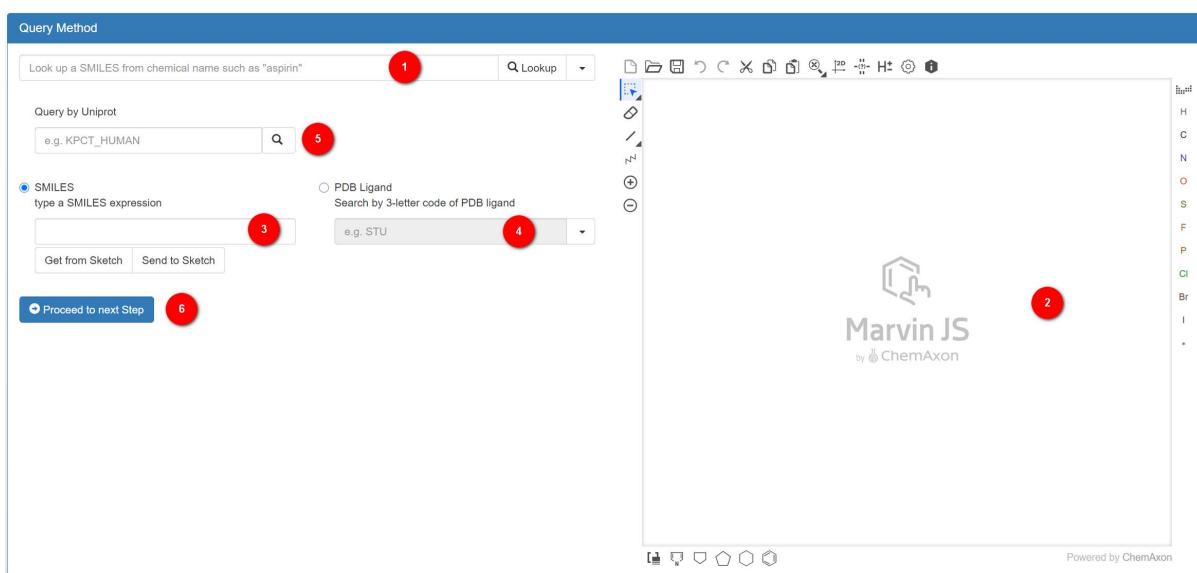
Uniprot & Variants	Pathways	Target Protein	PDB	Resolution(Å)	Chain	Affinity(µM)
POABQ4	ecj:Y75_p0048 eco:b0048	DYR_ECOLI	2INQ	2.2	<input type="checkbox"/> A <input type="checkbox"/> B	

Showing 1 to 1 of 1 entries

Either way, once clicking on the item corresponds to a particular ligand, the system will take you to the PDBs that are found in complex with the input ligands. If any compound has some text matches by the chemical names, multiple PDB 3-letter ligand codes will appear for further analysis.

4. Query Methods

After clicking access to MANORAA, the input panels will appear in the main page as follows.

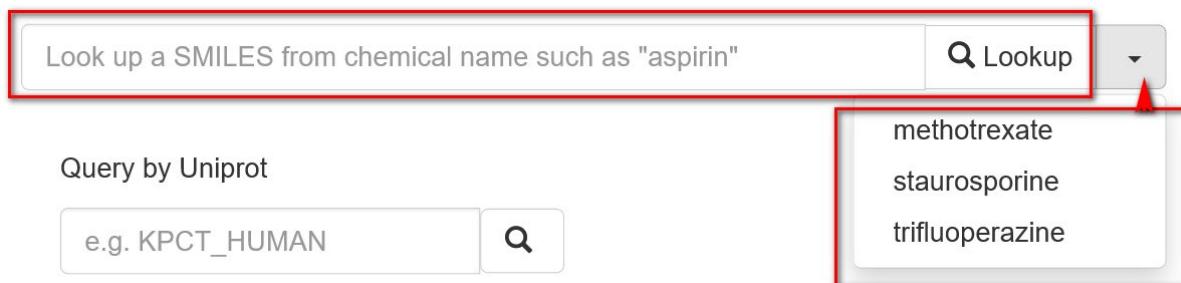


The data to be submitted to the next step can be in 2 entry forms, either by the SMILES string or by the ligand code. The query form will facilitate the user to submit a proper input format for MANORAA in various forms.

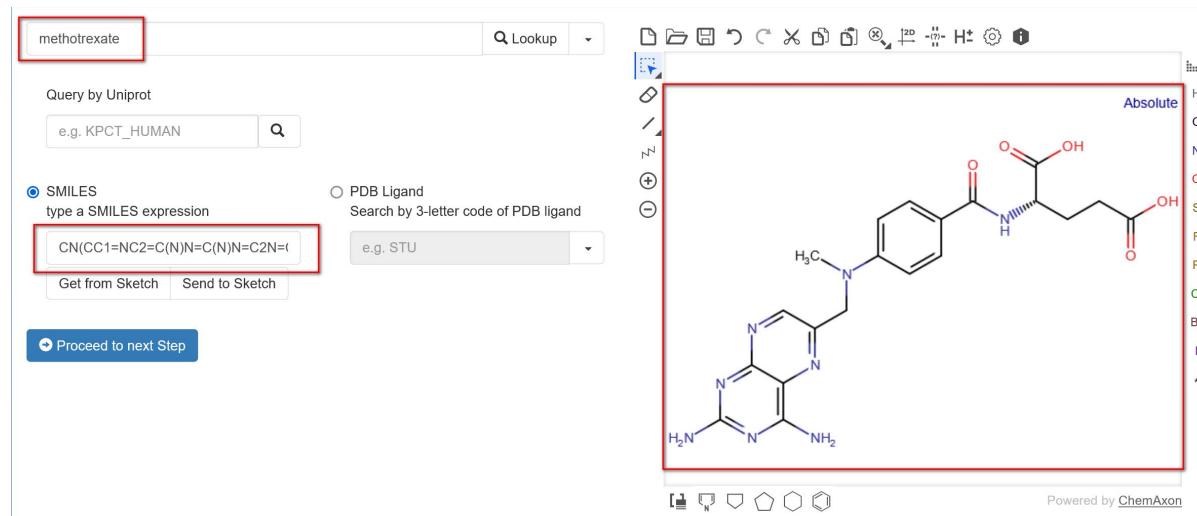
- (1) Chemical name: This input box will allow human readable words that match the drug name and transform it into a SMILES string and also the 2D sketch chemical sketch on the right panel.
- (2) Sketch: This tool permits the users to draw any chemical compounds or its fragments which can be translated into the SMILES string by the “Get from Sketch” button.
- (3) SMILES: This box allows the user to enter the whole SMILES string to match with the chemical compound database
- (4) PDB Ligand: This box allows input ligand in the form of PDB’s ligand 3-letter code
- (5) Query by Uniprot: This box allows searching of the protein’s UNIPROT code.
- (6) From selecting the option above, then the user can click "Proceed to next step".

Entering input with Chemical name

Users can search by entering information in the search box and then tap on the Lookup symbol. The system will display SMILES string information that users just search for. As example, user can select from a list of drug names as shown in the Dropdowns.

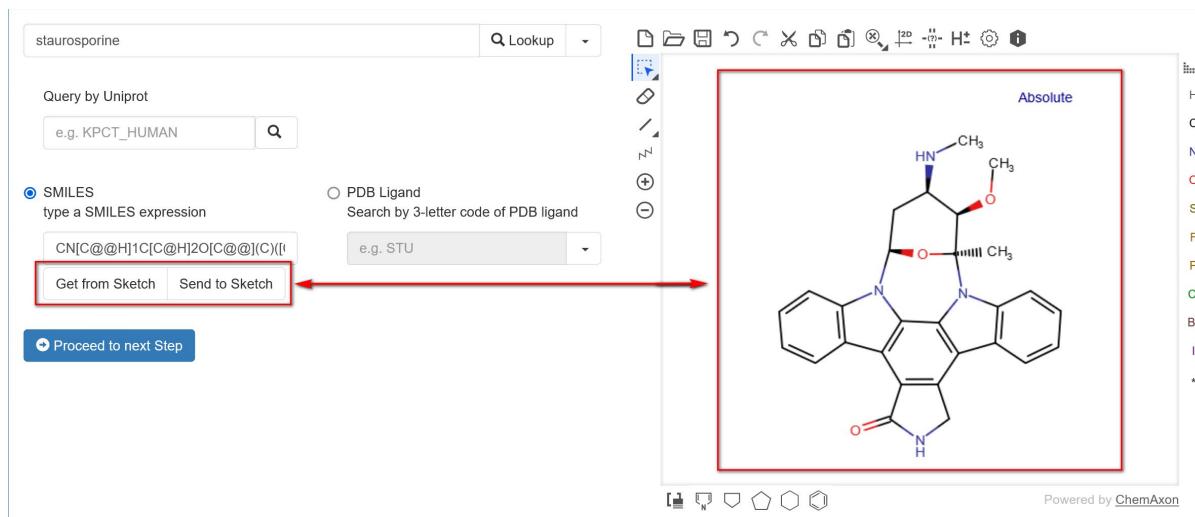


When the user presses search by drug name, the system will automatically search and put its SMILES data into the input box below and as well as a chemical sketch on the panel Sketch on the right hand side.



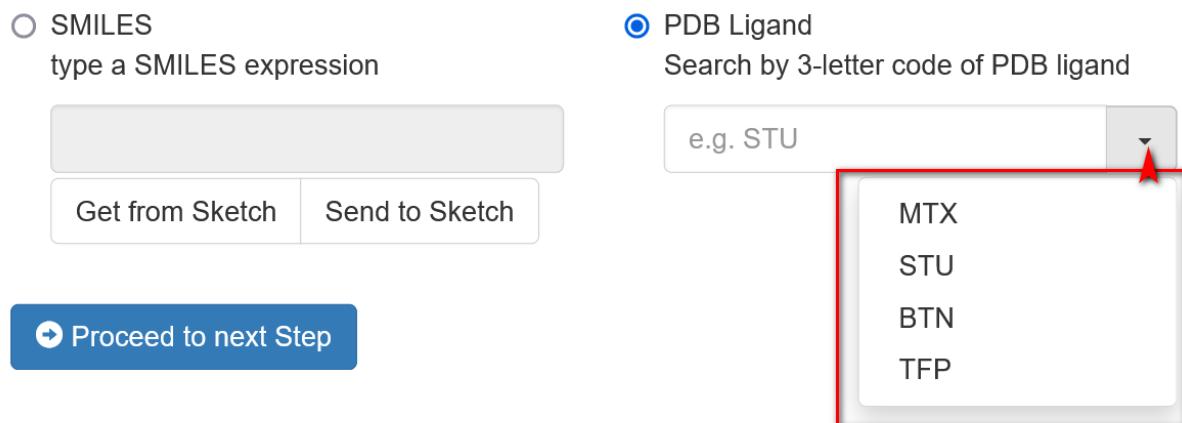
Entering input with Sketch and SMILES

Users can input data in the form of a SMILES string directly to be sent to the next step. Alternatively, users can draw a chemical sketch and convert it to SMILES. The SMILES input box and the Sketch panel can convert the data and send them back and forth with the "Get from Sketch" and "Send to Sketch" buttons.



Entering input with PDB Ligand

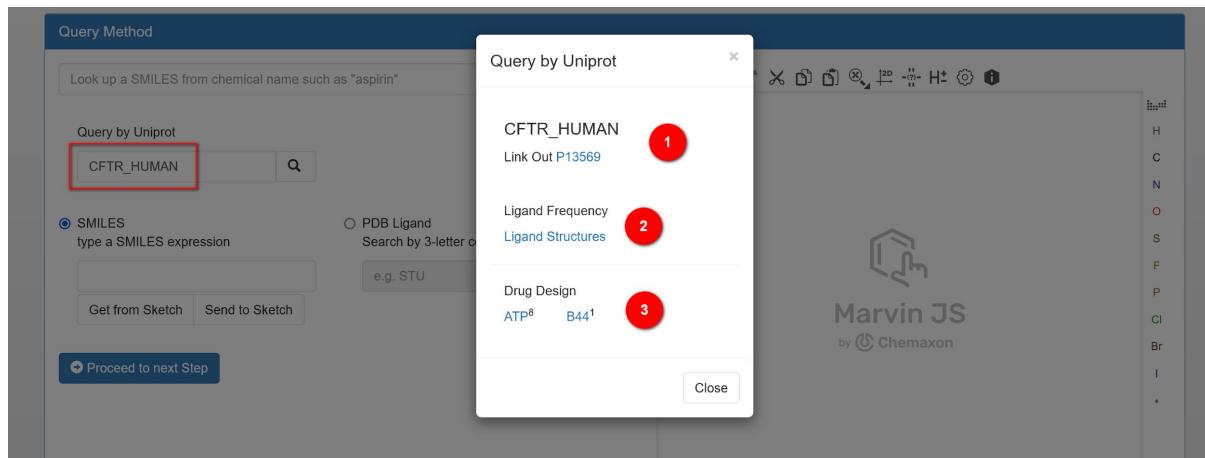
Users can enter the PDB Ligand 3-letter code directly into the input field to proceed.



As shown in the figure above, these are examples that can be chosen from a list of provided ligand three-letter codes.

Searching with the Query by UniProt function

Query by UniProt will search for proteins by Uniprot ID and will show a pop-up as follows.



Pop-up components are as follows:

- (1) Link Out is a function to bring up the link to <https://www.uniprot.org> by the UniProt ID that the user just searched.
- (2) Ligand Frequency is a screen to display ligand structures and PDB Chains according to the list of all Ligands for each UniProt ID. The button will call the Ligand Frequency function.
- (3) Drug Design displays a list of all Ligands of the searched UniProt ID, as sorted by searched Ligand's ID counts in descending orders. Under the Drug Design function of the Ligand, the program will select its substructure automatically, and overlay them accordingly.

5. Selection of atoms and PDB Chains

Filter by Categories

1

Uniprot ID	Pathway	UniProt Acc	PDB	Resolution(Å)	Chain	Affinity(µM)
------------	---------	-------------	-----	---------------	-------	--------------

Ligand Structure

PDB Chains

Uniprot &SNPs	Pathways	Target Protein	PDB	Resolution(Å)	Chain	Affinity(µM)
P59071		PA2B8_DABRR	3H1X	1.4	<input checked="" type="checkbox"/> A	3
P37231	hsa:5468	PPARG_HUMAN	3ADS	2.3	<input checked="" type="checkbox"/> A <input type="checkbox"/> B	9.73
Q9CP0U0	mmu:109801	LGUIL_MOUSE	4KYK	2.0	<input checked="" type="checkbox"/> B	18
Q9EQZ5		PTGR1_CAVPO	2DM6	2.0	<input checked="" type="checkbox"/> A	97.9
P24627	bta:280846	TRFL_BOVIN	3IB1	2.2	<input checked="" type="checkbox"/> A	260
D0VX11		D0VX11_9SAUR	3FQ7	1.4	<input type="checkbox"/> A	
P52895	hsa:101930400 hsa:1646	AK1C2_HUMAN	4JQ4	1.5	<input type="checkbox"/> A <input type="checkbox"/> B	
P42330	hsa:8644	AK1C3_HUMAN	3UGR	1.6	<input type="checkbox"/> A	
P42330	hsa:8644	AK1C3_HUMAN	1S2A	1.7	<input type="checkbox"/> A	
P42330	hsa:8644	AK1C3_HUMAN	3UG8	1.7	<input type="checkbox"/> A	
P60025	bta:280844	PERL_BOVIN	3OGW	1.9	<input type="checkbox"/> A	
Q8NQ7	hsa:145482	PTGR2_HUMAN	2ZB8	2.0	<input type="checkbox"/> A <input type="checkbox"/> B	
P37231	hsa:5468	PPARG_HUMAN	3ADX	2.0	<input type="checkbox"/> A <input type="checkbox"/> B	
P02766	hsa:7276	TTHY_HUMAN	4IKI	2.0	<input type="checkbox"/> A <input type="checkbox"/> B	
Uniprot &SNPs	Pathways	Target Protein	PDB	Resolution(Å)	<input type="checkbox"/> Chain	Affinity(µM)

2

IMN

Select substructures: Heteroatom:

N O O1 O2 O3
 All
 C C1 C2 C3 C4
 C5 C6 C7 C8 C9
 C10 C11 C12 C13 C14
 C15 C16 C17 C18 C19
 All

3

Showing 1 to 22 of 22 entries

Structural Conservation Protein-Ligand Interaction Binding-Distance Correlation Drug Design

After the users entering input in the form on the Query Method page, and then obtaining the desired SMILES string or Ligand code, user can press the "Proceed to next Step" button. It will take the user to the Ligand structure and PDB Chains page. This page will list all PDBs in the tabulated forms according to the entered ligand code. If the input data is a SMILES string, the system will search and list all matching ligands in each separated table on the screen.

The Ligand structure and PDB Chains page consists of three sections.

(1) Filtering Options are used to filter the columns in the table.

(2) Ligand substructures: The atom items can be selected in this panel in order to be used for the protein overlay.

(3) PDB Chains table: The PDB list are displayed. The user can select the PDB they want to overlay for the next structural analyses.

MANORAA System will automatically select Hetero-atoms and PDB with binding affinity as a default mode. The preliminary analysis can be done quickly by selecting all heteroatoms and selecting the first chain of the PDB that contains Binding Affinity value data under this default mode, and adjust the parameters later on after the users obtained enough information of what to look at from the first screen.

Filtering Options

Users can enter data into the desired filter fields. The system will display a list of recommended matches to select and filter in the display table.

Target Protein	PDB	Resolution(Å)	Chain	Affinity(µM)
DYR_HUMAN	1U72	1.9	<input checked="" type="checkbox"/> A	0.0000034
DYR_HUMAN	1DLS	2.3	<input checked="" type="checkbox"/> A	0.0109
DYR_HUMAN	3EIG	1.7	<input checked="" type="checkbox"/> A	0.021

PDB Chains table

Data in the PDB Chains display table includes UniProt, Pathways, Target Protein, PDB, Resolution, protein chain, and binding affinity.

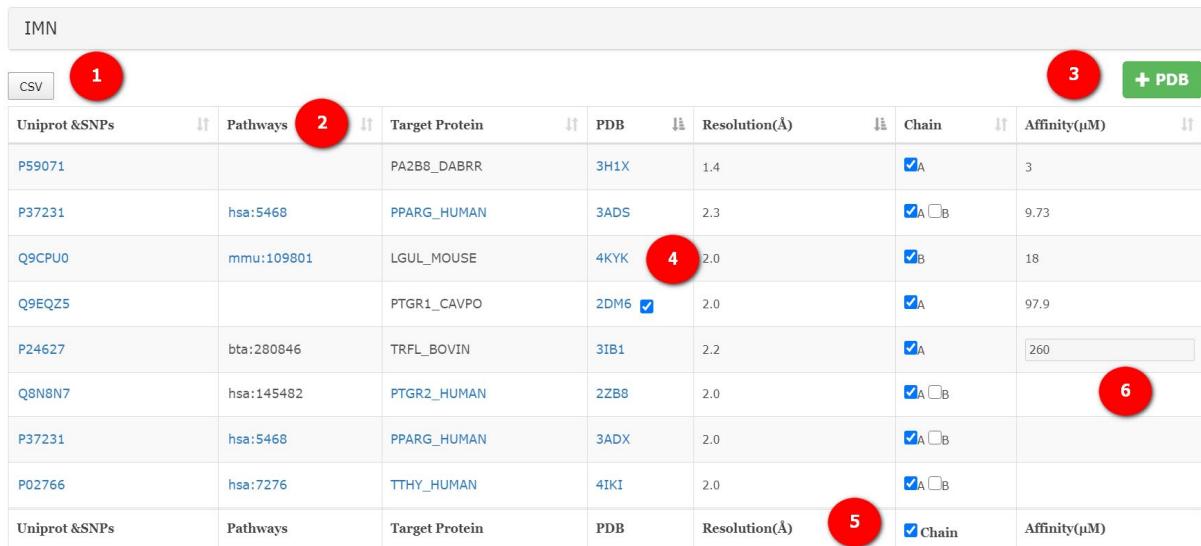
MANORAA matches PDB ID with various databases and provides a shortcut to link to the related websites such as:

<https://www.uniprot.org/>

<https://opentargets.org/>

<https://www.genome.jp/>

<https://www.ebi.ac.uk/>



The screenshot shows a table titled 'IMN' with the following columns: Uniprot & SNPs, Pathways, Target Protein, PDB, Resolution(Å), Chain, and Affinity(µM). The table contains 10 rows of data. Red circles with numbers 1 through 6 are overlaid on the interface to highlight specific features:

- 1**: CSV button in the top left corner.
- 2**: Up and down arrows in the Pathways and Target Protein columns, indicating sorting functionality.
- 3**: '+ PDB' button in the top right corner.
- 4**: A red circle with a number 4 is placed over the 'Chain' column header.
- 5**: A red circle with a number 5 is placed over the 'Affinity(µM)' column header.
- 6**: A red circle with a number 6 is placed over the 'Affinity(µM)' column header in the last row.

The components of the PDB Chains display table are as follows:

- (1) Save as CSV – Convert table data and download it as a comma-separated value (.csv) file.
- (2) Sorting – pressing these arrows to sort data in each column.
- (3) Upload – Button "+PDB" is used for uploading PDB to be used in various functions of the system.
- (4) Template – Select the PDB to be used as the template for the protein overlay.
- (5) Select All – this button can be pressed to select the first chain of every PDB.

(6) Affinity – The user can add or edit binding affinity value for a custom set of user input structural data.

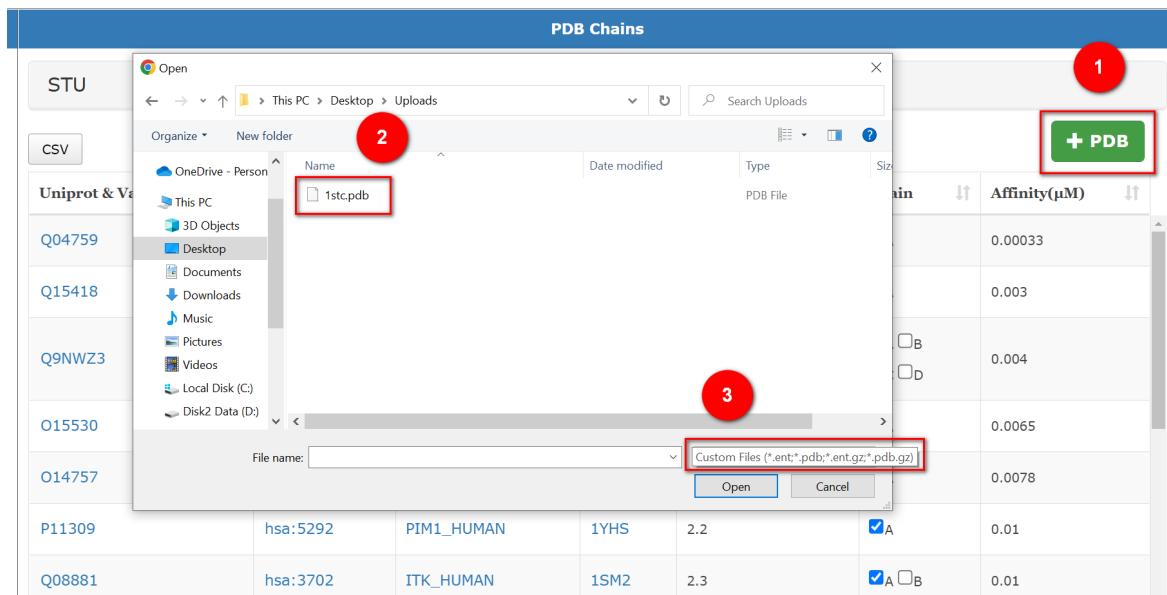
Save as CSV function

Sample data from the file MTX_pdb_chains.csv that are exported from the PDB Chains display table looks like below.

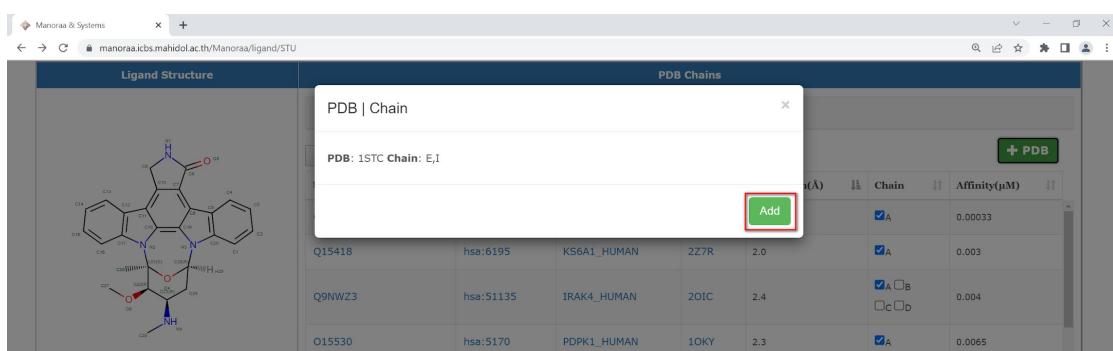
Uniprot & Variants	Pathways	Target Protein	PDB	Resolution(Å)	Chain	Affinity(μM)
P00374	hsa:1719 KEGG Pathway: hsa00670 One carbon pool by folate - Homo sapiens (human) hsa00790 Folate biosynthesis - Homo sapiens (human) hsa01100 Metabolic pathways - Homo sapiens (human) hsa01523 Antifolate resistance - Homo sapiens (human)	ANIMAL_HUMAN	1U72	1.9	A	0.0000034
P00374	hsa:1719 KEGG Pathway: hsa00670 One carbon pool by folate - Homo sapiens (human) hsa00790 Folate biosynthesis - Homo sapiens (human) hsa01100 Metabolic pathways - Homo sapiens (human) hsa01523 Antifolate resistance - Homo sapiens (human)	ANIMAL_HUMAN	1DLS	2.3	A	0.0109
P00374	hsa:1719 KEGG Pathway: hsa00670 One carbon pool by folate - Homo sapiens (human) hsa00790 Folate biosynthesis - Homo sapiens (human) hsa01100 Metabolic pathways - Homo sapiens (human) hsa01523 Antifolate resistance - Homo sapiens (human)	ANIMAL_HUMAN	3EIG	1.7	A	0.021
P14207	hsa:2350 KEGG Pathway: hsa01523 Antifolate resistance - Homo sapiens (human) hsa04144 Endocytosis - Homo sapiens (human)	FOLR2_HUMAN	4KNO	2.1	A	0.04

Upload function

Users can upload the desired PDB file to be used with various functions in the system by pressing the "+PDB" button. Then users can select the desired file from their own computer and press "Open". The structural data that can be uploaded are in the .ent, .pdb, .ent.gz and .pdb.gz file format with a maximum size of 25 MB.



The screen will show the PDB and Chain which are retrieved from the imported data file. Once the structure file is validated, press the Add button to add it to the table.



The uploaded PDB data will be added to the table for selection.

Ligand Structure		PDB Chains																																																							
<p>STU Select substructures:</p>		<p>STU</p> <p>CSV + PDB</p> <table border="1"> <thead> <tr> <th>Uniprot & Variants</th> <th>Pathways</th> <th>Target Protein</th> <th>PDB</th> <th>Resolution(Å)</th> <th>Chain</th> <th>Affinity(µM)</th> </tr> </thead> <tbody> <tr> <td>P43403</td> <td>hsa:7535</td> <td>ZAP70_HUMAN</td> <td>1U59</td> <td>2.3</td> <td><input checked="" type="checkbox"/> A</td> <td>0.0558</td> </tr> <tr> <td>P33981</td> <td>hsa:7272</td> <td>TTK_HUMAN</td> <td>3HMO</td> <td>2.4</td> <td><input checked="" type="checkbox"/> A <input type="checkbox"/> B</td> <td>0.102</td> </tr> <tr> <td></td> <td></td> <td></td> <td>★ 1STC</td> <td></td> <td><input type="checkbox"/> E <input type="checkbox"/> I</td> <td></td> </tr> <tr> <td>P53667</td> <td>hsa:3984</td> <td>LIMK1_HUMAN</td> <td>3S95</td> <td>1.6</td> <td><input checked="" type="checkbox"/> A <input type="checkbox"/> B</td> <td></td> </tr> <tr> <td>P07332</td> <td>hsa:2242</td> <td>FES_HUMAN</td> <td>3BKB</td> <td>1.8</td> <td><input type="checkbox"/> A</td> <td></td> </tr> <tr> <td>P07332</td> <td>hsa:2242</td> <td>FES_HUMAN</td> <td>3CBL</td> <td>1.8</td> <td><input type="checkbox"/> A</td> <td></td> </tr> </tbody> </table>							Uniprot & Variants	Pathways	Target Protein	PDB	Resolution(Å)	Chain	Affinity(µM)	P43403	hsa:7535	ZAP70_HUMAN	1U59	2.3	<input checked="" type="checkbox"/> A	0.0558	P33981	hsa:7272	TTK_HUMAN	3HMO	2.4	<input checked="" type="checkbox"/> A <input type="checkbox"/> B	0.102				★ 1STC		<input type="checkbox"/> E <input type="checkbox"/> I		P53667	hsa:3984	LIMK1_HUMAN	3S95	1.6	<input checked="" type="checkbox"/> A <input type="checkbox"/> B		P07332	hsa:2242	FES_HUMAN	3BKB	1.8	<input type="checkbox"/> A		P07332	hsa:2242	FES_HUMAN	3CBL	1.8	<input type="checkbox"/> A	
Uniprot & Variants	Pathways	Target Protein	PDB	Resolution(Å)	Chain	Affinity(µM)																																																			
P43403	hsa:7535	ZAP70_HUMAN	1U59	2.3	<input checked="" type="checkbox"/> A	0.0558																																																			
P33981	hsa:7272	TTK_HUMAN	3HMO	2.4	<input checked="" type="checkbox"/> A <input type="checkbox"/> B	0.102																																																			
			★ 1STC		<input type="checkbox"/> E <input type="checkbox"/> I																																																				
P53667	hsa:3984	LIMK1_HUMAN	3S95	1.6	<input checked="" type="checkbox"/> A <input type="checkbox"/> B																																																				
P07332	hsa:2242	FES_HUMAN	3BKB	1.8	<input type="checkbox"/> A																																																				
P07332	hsa:2242	FES_HUMAN	3CBL	1.8	<input type="checkbox"/> A																																																				

After selecting the desired atoms and the PDB ID, the user can press any of these green buttons below the table in order to use the functions they want.

STU Select substructures: Heteroatom: N1 <input checked="" type="checkbox"/> N2 <input checked="" type="checkbox"/> N3 <input checked="" type="checkbox"/> N4 <input checked="" type="checkbox"/> O4 O5 <input checked="" type="checkbox"/> O6 <input checked="" type="checkbox"/> All C1 <input type="checkbox"/> C2 <input type="checkbox"/> C3 <input type="checkbox"/> C4 <input type="checkbox"/> C5 C6 <input type="checkbox"/> C7 <input type="checkbox"/> C8 <input type="checkbox"/> C9 <input type="checkbox"/> C10 C11 <input type="checkbox"/> C12 <input type="checkbox"/> C13 <input type="checkbox"/> C14 <input type="checkbox"/> C15 C16 <input type="checkbox"/> C17 <input type="checkbox"/> C18 <input type="checkbox"/> C19 <input type="checkbox"/> C20 C21 <input type="checkbox"/> C22 <input type="checkbox"/> C23 <input type="checkbox"/> C24 <input type="checkbox"/> C25 C26 <input type="checkbox"/> C27 <input type="checkbox"/> C28 <input type="checkbox"/> All		<table border="1"> <tbody> <tr> <td>P11309</td> <td>hsa:5292</td> <td>PIM1_HUMAN</td> <td>1YHS</td> <td>2.2</td> <td><input checked="" type="checkbox"/> A</td> <td>0.01</td> </tr> <tr> <td>Q08881</td> <td>hsa:3702</td> <td>ITK_HUMAN</td> <td>1SM2</td> <td>2.3</td> <td><input checked="" type="checkbox"/> A <input type="checkbox"/> B</td> <td>0.01</td> </tr> <tr> <td>P43405</td> <td>hsa:6850</td> <td>KSYK_HUMAN</td> <td>1XBC</td> <td>2.0</td> <td><input checked="" type="checkbox"/> A</td> <td>0.012</td> </tr> <tr> <td>P49841</td> <td>hsa:2932</td> <td>GSK3B_HUMAN</td> <td>1Q3D</td> <td>2.2</td> <td><input checked="" type="checkbox"/> A <input type="checkbox"/> B</td> <td>0.015</td> </tr> <tr> <td>P43403</td> <td>hsa:7535</td> <td>ZAP70_HUMAN</td> <td>1U59</td> <td>2.3</td> <td><input checked="" type="checkbox"/> A</td> <td>0.0558</td> </tr> <tr> <td>P33981</td> <td>hsa:7272</td> <td>TTK_HUMAN</td> <td>3HMO</td> <td>2.4</td> <td><input checked="" type="checkbox"/> A <input type="checkbox"/> B</td> <td>0.102</td> </tr> <tr> <td>P53667</td> <td>hsa:3984</td> <td>LIMK1_HUMAN</td> <td>3S95</td> <td>1.6</td> <td><input type="checkbox"/> A <input type="checkbox"/> B</td> <td></td> </tr> <tr> <td>P07332</td> <td>hsa:2242</td> <td>FES_HUMAN</td> <td>3BKB</td> <td>1.8</td> <td><input type="checkbox"/> A</td> <td></td> </tr> </tbody> </table>							P11309	hsa:5292	PIM1_HUMAN	1YHS	2.2	<input checked="" type="checkbox"/> A	0.01	Q08881	hsa:3702	ITK_HUMAN	1SM2	2.3	<input checked="" type="checkbox"/> A <input type="checkbox"/> B	0.01	P43405	hsa:6850	KSYK_HUMAN	1XBC	2.0	<input checked="" type="checkbox"/> A	0.012	P49841	hsa:2932	GSK3B_HUMAN	1Q3D	2.2	<input checked="" type="checkbox"/> A <input type="checkbox"/> B	0.015	P43403	hsa:7535	ZAP70_HUMAN	1U59	2.3	<input checked="" type="checkbox"/> A	0.0558	P33981	hsa:7272	TTK_HUMAN	3HMO	2.4	<input checked="" type="checkbox"/> A <input type="checkbox"/> B	0.102	P53667	hsa:3984	LIMK1_HUMAN	3S95	1.6	<input type="checkbox"/> A <input type="checkbox"/> B		P07332	hsa:2242	FES_HUMAN	3BKB	1.8	<input type="checkbox"/> A	
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Uniprot & Variants	Pathways	Target Protein	PDB	Resolution(Å)	Chain	Affinity(µM)																																																										

Showing 1 to 52 of 52 entries

Structural Conservation **Protein-Ligand Interaction** **Binding-Distance Correlation** **Drug Design**

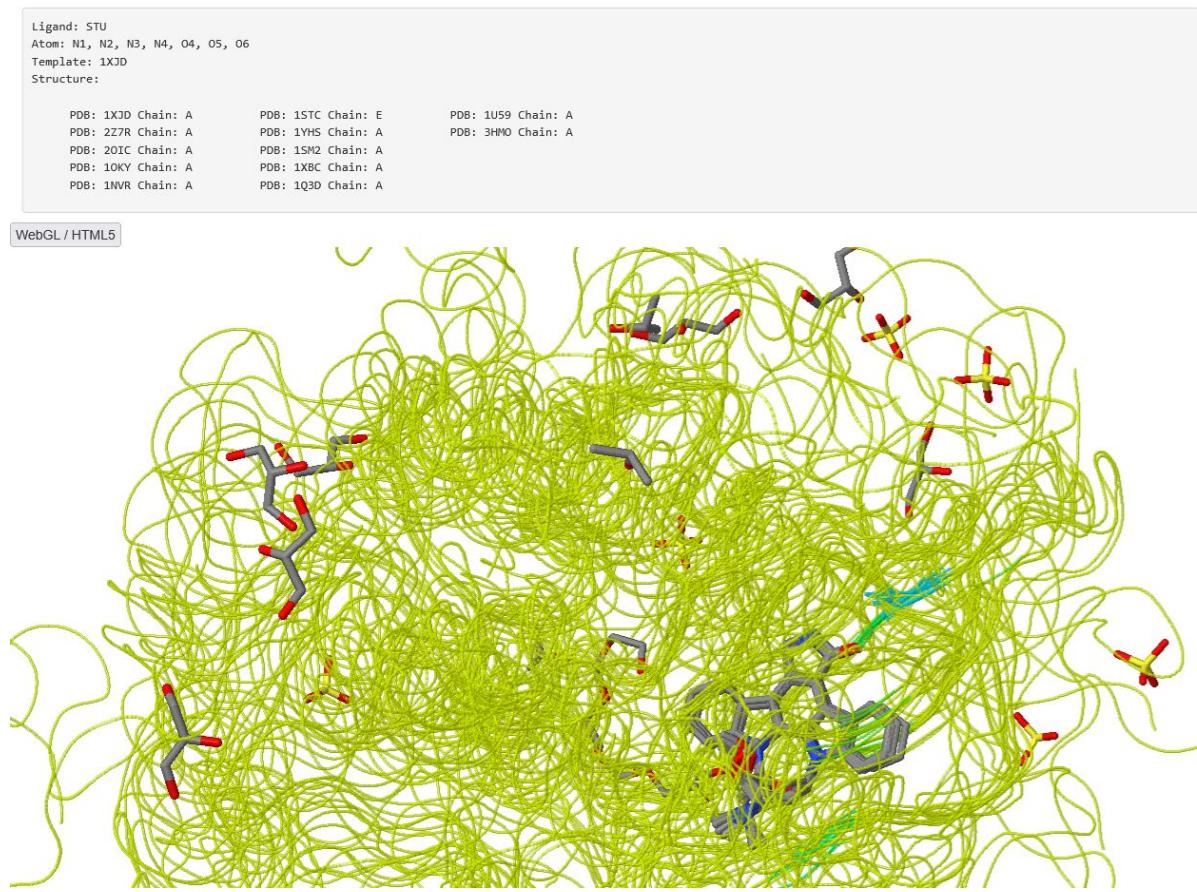
There are 4 types of functions available to use:

- Structural Conservation button
- Protein-Ligand Interaction button
- Binding-Distance Correlation Button
- Drug Design button

6. Structural Conservation Function

Jsmol protein superposition results are displayed in WebGL format. The selected ligand atom positions are overlaid and the points with the atoms deposited in the same position are displayed in blue. The gradient colour ranges from yellow to green and to blue as the number of atoms that are fallen into the bin increases. The most conserved entities are shown in blue.

Position-specific interaction by highlighting the active site based on the percent conservation of the atomic position surrounding the ligand substructure for STU superposed complexes.

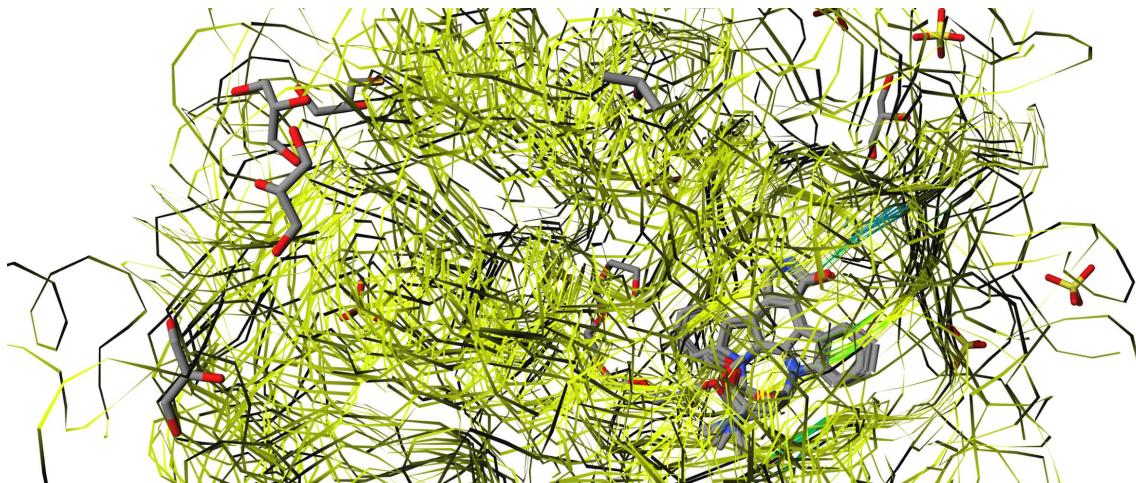


The Structural Conservation display consists of 2 parts.

- WebGL/HTML5 – Press to toggle between WebGL and HTML5.
- 3D Panel – The section used to show the overlay of proteins.

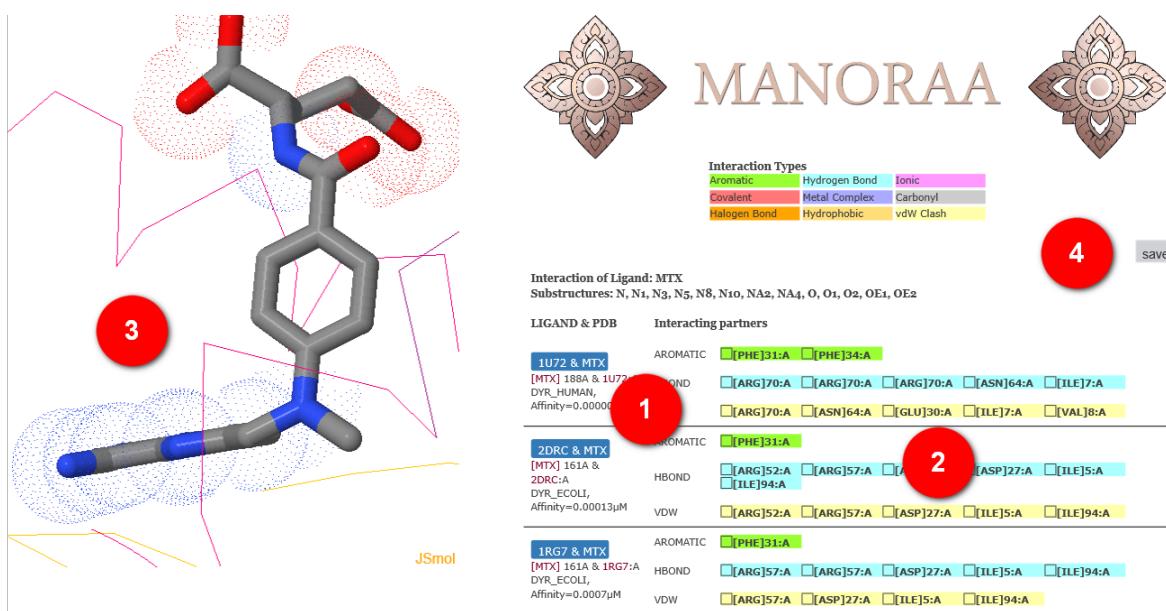
WebGL/HTML5

This button can render the overlay of the protein with either WebGL or JSmol in HTML5.



7. Protein-Ligand Interaction Function

The chosen atoms were used to calculate the protein-ligand interactions. The user can rank interactions that occurred between atoms and all the surrounding amino acid groups according to the binding affinity. For example, when the user sorts the binding affinities from lowest to highest, the numbers of hydrogen bonds can be found from the tightest bound to the loosely bound binding interactions.



The Protein-Ligand Interaction display consists of 4 sections.

- (1) PDB ID & Ligand – Press to display the selected PDB and ligand.
- (2) Residue – Select the Residue that you want to display.
- (3) 3D Panel - This panel is used to display the results.
- (4) Save – Press to save the screen as a .png image file.

8. Binding-Distance Correlation Function

It shows the amino acid position that is essential for drug binding, and the influential distances that affect the tightness of drug binding in the form of influential distance-binding equation. The distances are drawn on to the template structure with the anchoring point for distance measurement labeled at each end of the distance bar.

Multiple alignment and influential distance equation to correlate inter-residue distance with binding affinity.

Ligand: BAX
 Atom: F8, F9, F10, N12, N14, N26, N30, O15, O22, O32
 Template: 4ASD
 Structure:

PDB: 4ASD Chain: A
 PDB: 3GCS Chain: A
 PDB: 3HEG Chain: A
 PDB: 3RGF Chain: A

PDB	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15	B16	B17	B18
3GCS	ALA-302	ARG-149	ARG-23	ASN-115	ASP-150	ASP-168	ASP-205	GLU-71	GLY-85	HIS-148	HIS-77	HIS-80	ILE-131	ILE-141	ILE-166	ILE-84	LEU-104	LEU-113
3HEG	ALA-302	ARG-149	ARG-23	ASN-115	ASP-150	ASP-168	ASP-205	GLU-71	GLY-85	HIS-148	HIS-77	HIS-80	ILE-131	ILE-141	ILE-166	ILE-84	LEU-104	LEU-113
3RGF	GLU-327	ARG-150	ARG-40	ILE-107	ASP-151	ASP-173	ASP-216	GLU-66	SER-80	HIS-149	ARG-71	HIS-75	LEU-136	LEU-142	ILE-171	ILE-79	LEU-95	LEU-104
*4ASD	SER-1154		ARG-1027		PHE-854	TYR-927	ASP-1028		ASP-1046		ASP-1087		GLU-885	ASN-900	HIS-1026		ILE-890	HIS-895

Influential Distance:
 $\text{Log10}K_i = -19.9127 + 0.5207 \times D(B16, B1) + 0.3484 \times D(B20, B27)$

3GCS

The Binding-Distance Correlation display screen consists of 2 parts.

- (1) PDB ID – Choose the PDB you want to display.
- (2) 3D Panel - This part is used to display the results.

9. Drug Design Function

It shows the position that is essential for drug binding, the distance that influences the tightness of drug binding and distance-binding affinity equation. The image of the protein overlay results can also be displayed according to the various selected options.

The Drug Design display screen consists of 2 parts.

- (1) Option buttons on the left hand side, which can be chosen to display in different functions.
- (2) 3D Panel - The part used to display the results.

Position-specific interaction by highlighting the active site based on the percent conservation of the atomic position surrounding the ligand substructure complexes.

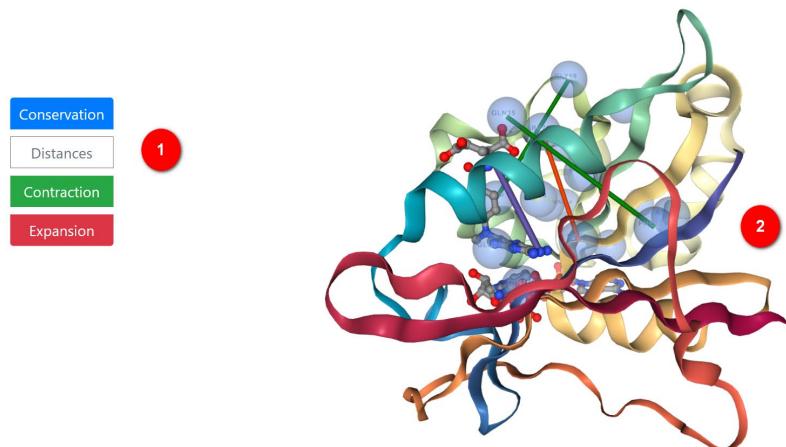
Ligand: MTX
 Atom: N, N1, N3, N5, N8, N10, NA2, NA4, O, O1, O2, OE1, OE2
 Template: 1U72
 Structure:

PDB: 1U72 Chain: A	PDB: 2QK8 Chain: A
PDB: 1RG7 Chain: A	PDB: 3EIG Chain: A
PDB: 3DFR Chain: A	PDB: 4KN0 Chain: A
PDB: 1DLS Chain: A	PDB: 1U70 Chain: A
PDB: 1DF7 Chain: A	

PDB B1 B2 B3 B4 B5 B6 B7 B8 B9 B10 B11 B12 B13 B14 B15 B16 B17
 1DF7 ARG-32 ARG-60 ARG-61 ASN-62 ASP-27 GLU-111 GLY-3 GLY-59 ILE-5 LEU-65 MET-42 PHE-31 PRO-51 THR-113 THR-35 VAL-64 VAL-78
 1DLS GLN-35 ARG-70 ILE-71 ASN-72 GLU-30 PHE-134 ASN-5 GLY-69 ILE-7 LEU-75 MET-52 PHE-34 ILE-60 THR-136 THR-38 VAL-74 SER-90
 1RG7 LYS-32 ARG-57 LYS-58 ASN-59 ASP-27 TYR-111 SER-3 GLY-56 ILE-5 LEU-62 MET-42 PHE-31 ILE-58 THR-113 THR-35 ILE-61 VAL-75
 1U70 GLN-35 ARG-70 ILE-71 ASN-72 GLU-30 PHE-134 ASN-5 ASP-69 ILE-7 LEU-75 MET-52 PHE-34 ILE-60 THR-136 THR-38 VAL-74 ALA-90
 *1U72 GLN-35 ARG-70 ILE-71 ASN-72 GLU-30 PHE-134 ASN-5 GLY-69 ILE-7 LEU-75 MET-52 PHE-34 ILE-60 THR-136 THR-38 VAL-74 SER-90
 2QK8 LYS-33 ARG-58 ARG-59 ASN-60 GLU-28 TYR-113 SER-4 GLY-57 MET-6 VAL-63 MET-43 PHE-96 ILE-51 THR-115 THR-36 ILE-62 ALA-77
 3DFR ARG-31 ARG-57 THR-58 ASN-59 ASP-26 LEU-114 ALA-2 GLU-56 LEU-4 LEU-62 VAL-41 PHE-30 PHE-49 THR-116 THR-34 VAL-61 VAL-76
 3EIG GLU-35 ARG-70 ILE-71 ASN-72 GLU-30 PHE-134 ASN-5 GLY-69 ILE-7 LEU-75 MET-52 PHE-34 ILE-60 THR-136 THR-38 VAL-74 SER-90
 4KN0 ARG-152 LYS-147 CYS-146 HIS-82 ARG-122 TYR-191 LEU-182 PRO-164 LEU-186 LYS-91 TRP-80 TRP-187 ASN-77 PHE-123 ASN-149 ASP-81 LYS-85

Influential Distance:
 $\text{Log10} Ki = -4.5618 - 0.5868 \times D(B2, B9) + 0.3482 \times D(B6, B1) + 0.1937 \times D(B8, B13)$

1U72



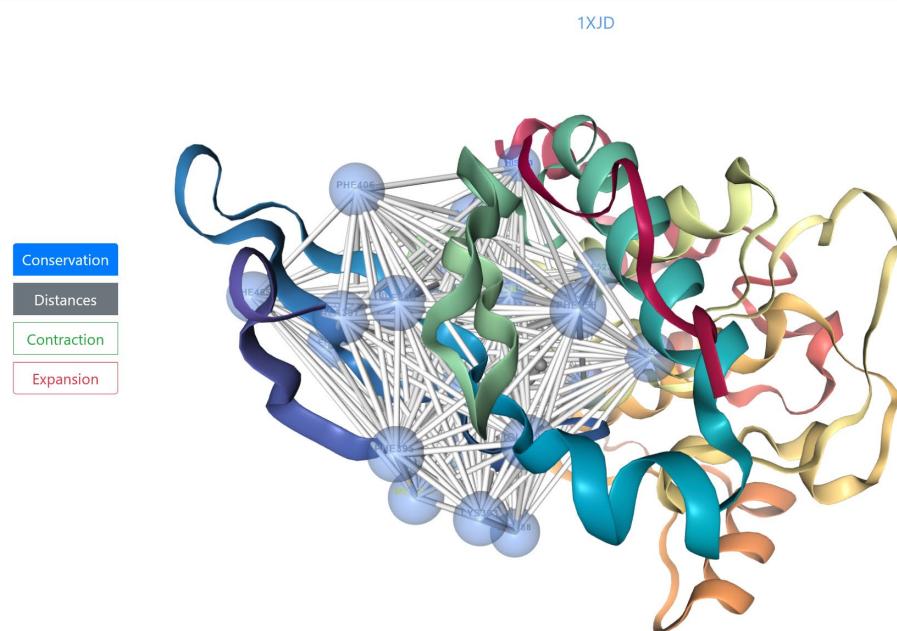
Options display format

Users can choose from 4 different display formats as follows:

- Conservation: returns position-specific positions that are Structurally Conserved Entities.
- Distances: shows all distances included in the calculation which are all positions that fall in the bin.

- Contraction: shows influential distances from the pocket with a preference for pocket contraction along this direction
- Expansion: shows influential distances from the pocket with a preference for pocket expansion for a better drug binding.

An example when displaying all distances with all atomic positions that are Structural Conservation Entities.



10. Web Services API

Servers: <https://manoraa.icbs.mahidol.ac.th>

Method	Path	Description	Type
GET	/Manoraa/api/ligand/{3-letter code}	Get information on Ligand Substructures and PDB Chains.	JSON

Example response:

```
[
  {
    "Ligand": "MTX",
    "PDB Chains": [
      {
        "Uniprot &SNPs": "076290",
        "Pathways": [
          ""
        ],
        "Target Protein": "076290_TRYBB",
        "PDB": "2C7V",
        "Resolution(Å)": 2.2000005,
        "Chain": [
          "A",
          "B",
          "C",
          "D"
        ],
        "Affinity(µM)": "0.000000152"
      },
      {
        "Uniprot &SNPs": "P00374",
        "Pathways": [
          "hsa:1719"
        ],
        "Target Protein": "DYL_HUMAN",
        "PDB": "1DLS",
        "Resolution(Å)": 2.2999995,
        "Chain": [
          "A"
        ],
        "Affinity(µM)": "0.0000000109"
      }
    ]
  }
]
```