DATE: 08/10/2022

WEBLEM 5

Introduction to Pharmacophore mapping

When the 3D structure of the protein target has not been characterized, and/or when a certain number of ligands (with or without associated binding affinity) are available, pharmacophore models can be developed and used as search queries for virtual screening of databases. Pharmacophore models may range from sub-structural type pharmacophores to feature- based pharmacophores, in the latter the pharmacophoric points are represented by chemical features like hydrogen - bond acceptors/donors, hydrophobic points, acidic or basic features etc. Moreover, when the necessity occurs to move to the 3D level, virtual screening has to deal with enhanced complexity with regard to functionality and flexibility of molecules, which requires more sophisticated tools for analyzing this type of data. For implementation of this concept into virtual screening, the chemical function-based approach is the most generic one. The originality of this type of pharmacophores mostly resides in the fact that their definition is general and represents different types of interactions between organic molecules and proteins. The utility of such models as queries for 3D database search has been recently reviewed. Such pharmacophores can be generated indifferently from ligand sets or from an active site structure. At the end of virtual screening filtering procedure, a reliable method for ranking the hits obtained according to their expected bioactivity is required.

Methods for Pharmacophore Generation There are two ways to deduce a pharmacophore: direct- and indirect-methods. The former uses both the ligand and the receptor information, while the latter employs only a collection of ligands that have been experimentally observed to interact with a given receptor. Indirect methods can be used even in the absence of structure of the receptor and hence are more advantageous in the present scenario where the crystal structures of less than 10 % of drug targets are available. However, direct methods are becoming extremely important with the rapidly increasing number of known protein structures, which is the outcome of the Structural Genomics project. Once identified, a pharmacophore model is a versatile tool for the discovery and development of new lead compounds. Steps in Identifying a Pharmacophore In general, all the algorithms for pharmacophore identification utilize the following six steps:

1) Input

2) Conformational Search

3) Feature extraction

4) Structure Representation

5) Pattern Identification

6) Scoring

PharmMapper:

PharmMapper server is a freely accessed web server designed to identify potential target candidates for the given small molecules (drugs, natural products or other newly discovered compounds with unidentified binding targets) using pharmacophore mapping approach. PharmMapper hosts a large, in-house repertoire of pharmacophore database (namely PharmTargetDB) annotated from all the targets information in TargetBank, BindingDB, DrugBank and potential drug target database, including over 7000 receptor-based pharmacophore models (covering over 1500 drug targets information). PharmMapper automatically finds the best mapping poses of the query molecule against all the pharmacophore models in PharmTargetDB and lists the top N best-fitted hits with appropriate target annotations, as well as respective molecule's aligned poses are presented. Benefited from the highly efficient and robust triangle hashing mapping method, PharmMapper bears high throughput ability and only costs 1 h averagely to screen the whole PharmTargetDB.

WORKING:

Construction of potential targets pharmacophore databases

PharmMapper requires a sufficient number of available pharmacophore models describing the binding modes of known ligands at the binding sites of protein targets. The target protein structures co-complexed with small molecules were carefully selected from DrugBank, BindingDB, PDBBind and our PDTD databases. DrugBank hosts a complete list of known targets with appropriate annotations, while BindingDB and PDBBind provide public, web-accessible databases of measured binding affinities, focusing chiefly on the interactions of those proteins considered to be drug targets with small or drug-like molecules. Only those proteins with available 3D crystal structures were selected and used for pharmacophore model extraction.

LigandScout, which is a software tool that allows rapid extraction of 3D pharmacophores from structural data of macromolecule–ligand complexes in a fully automated and convenient way, was used in the process of pharmacophore model derivation. Six primary types of pharmacophore features were adopted in this process: hydrophobic center (H), positive-charged center (P), negative-charged center (N), hydrogen bond acceptor vector (HBA), hydrogen bond donor vector (HBD) and aromatic plane (AR) and one optional feature [metal interaction center (M)]. Each ligand binding site was manually analyzed after generation of corresponding pharmacophore model and the corresponding shape was characterized by several excluded volumes centered at each residue of the binding pocket. All the small ligands with molecular weight lower than 100, such as solvents, buffers and metal cations, and all the cofactors with molecular weight over 600, such as CoAs, polypeptides and nucleic acids were regarded as 'environment atoms' instead of binding ligands. In this context, the corresponding pharmacophore models were not generated. For the proteins existing as homopolymers, only one monomer was reserved for analysis. For the proteins determined by NMR with multiple structure models, only the first model was selected for pharmacophore generation. As a result, we generated 7302 pharmacophore models (2241 entries are annotated as 'Human protein targets') and deposited them in PharmTargetDB. The target annotations were extracted from DrugBank, PDBSum, UniProt and in-house TargetBank (our unpublished data) and were categorized as follows: UniProt access ID, target name, target function and indication/disease involved.

Reverse pharmacophore mapping procedure using PharmMapper

PharmMapper consists of two parts: a front-end web interface written in both PHP and HTML, with MySQL as database system, and a back-end tool for reverse pharmacophore mapping. The reverse pharmacophore mapping procedure is as follows: (i) PharmMapper flexibly aligns the given small molecule onto each pharmacophore model of proteins in the target list, and the fit values between the small molecule and the pharmacophores are calculated and recorded; (ii) PharmMapper presents the aligned pose with the corresponding pharmacophore model and prioritizes candidate targets based on the fit values to analyze the reverse mapping result. In general, PharmMapper outputs the top N hits of the ranking list, from which the user may select protein candidates for further bioassay validation.

Generally, the algorithm suggests to solve the molecule pharmacophore best fitting task in a strategy of sequential combination of triangle hashing (TriHash) and genetic algorithm (GA) optimization, which consists of following major steps: (i) ligand initialization and preparation; (ii) ligand as well as target pharmacophore model features triangulation; (iii) pairwise alignment and GA post optimization; and (iv) solution filtering, ranking and output. The readers can refer to the Supplementary Data for more details about the pharmacophore mapping algorithm used by PharmMapper.

PharmMapper server is open-accessed and free of charge. Users are expected to upload the mol2 file of the test molecule, customize the mapping parameters and submit a job. A job identity number, namely the JOB ID, is assigned to each job by the web server, and the number is appended to a job queue in the back-end server. The user may use the JOB ID to check the status of the submitted job.

Input

PharmMapper's interface is very simple. Its input form has only one mandatory field: a file with single drug-like molecule or natural product stored in Mol2 format. The user must make sure the uploaded molecule has appropriate 3D structural information. Multiple commercial or open source toolkits are recommended to complete this task, including CORINA, CONCORD and ChemAxon's Standardizer. The user can choose or not to leave an email address in order to receive a notification when the job is finished. After uploading the file, the user is encouraged to set some optional parameters in the following pop-up form instead of accepting corresponding default values to reduce the computational cost or achieve more accurate result. Since PharmMapper uses semi-flexible alignment strategy, a conformer ensemble has to be generated prior to mapping. For single 3D conformer provided by the user, an in-house program Cyndi is used by default to generate multiple conformations. Of course, the user can skip this step by uploading pre-generated conformation ensemble with other programs, such as CAESAR, MacroModel and Omega. Additionally, the user can specify the minimum number of each pharmacophore feature type to skip those target pharmacophore models, of which the number of corresponding pharmacophore features are less than the threshold values. Moreover, the scoring weights assigned to each type of pharmacophore feature can be adjusted according to the user's judgment towards the structural, physicochemical features presented by the molecule (e.g. if the molecule bears dominantly hydrophobic features, the scoring weight assigned to the Hydrophobic Score can be moderately increased to favor the hydrophobic interaction with the pharmacophore models). Detailed explanations for each field can be displayed in the pop-up windows when the mouse is lifted on the corresponding field and are also available in the Help page.

Output

A typical run of PharmMapper task takes 1–2 h, depending on the flexibility of the input molecule and filter parameters assigned by the user. To ensure successful job submission, the user is prompted to activate a self-refreshed alert page to monitor the job status. The user can bookmark this alert page so as to check the status of corresponding job at any time in the feature. Once the job completes, the user is automatically redirected to the computational results via the self-refreshed page or expected to input the JOB ID in the 'Get Result' page to access the computational results. The hyperlink to the result page is also contained in the notification after the job is finished, if the users have left their email address during job submission. The result will be kept on the server for up to 3 months so that the user may access the result at any time later via the same JOB ID.

The output of a PharmMapper run is demonstrated in the form of a ranked list of hit target pharmacophore models that are sorted by fit score in descending order. User can also re-rank the result list by normalized fit score or number of pharmacophore features in descending order via clicking the arrow icons in the corresponding columns. The 3D structural information can be accessed via the hyperlinks in the 'PDB ID' column to the Protein Database Bank (PDB) website. The hotlink to UniProt database as well as functional and therapeutic annotations of each target will be presented in the pop-up window by mouse lifting over the corresponding PDB IDs. As Figure 1B shows, a pull-down window will appear by clicking the '+' mark at the starting of each line of the result table, which illustrates the details of each pharmacophore model candidate, including the numbers of each pharmacophore feature (rendered in different colors scheme), a 3D interactive visualization of molecule-pharmacophore alignment poses displayed via a modified version of Jmol applet (http://www.jmol.org), and the download links of the aligned pose of molecule as well as the corresponding pharmacophore model (in hypoedit format). The radio buttons in the pull-down window allow the users to show/hide either the pharmacophore model, query molecular conformation or the features from the query molecule in display, which may provide better visual assessment for the matching quality between the input probe molecule and the identified potential target pharmacophore models. All the text-based targets information is downloadable in comma separated values (CSV) format via the hotlink at the bottom of the result page.

ZINCPharmer:

A pharmacophore describes the structural arrangement of the essential molecular features of an interaction between a ligand and its receptor. Searching chemical libraries for compounds that match a specific pharmacophore is an established method of virtual screening. The two main challenges of pharmacophore-based virtual screening are identifying a representative pharmacophore for an interaction and then identifying the compounds within a relevant chemical library that match the pharmacophore. ZINCPharmer is a pharmacophore search engine for purchasable chemical space that addresses both these challenges.

An interaction pharmacophore may be elucidated from a set of known active ligands by identifying a consensus pharmacophore that is conformationally accessible to all these ligands. These techniques do not require a ligand-bound structure, but may be computationally demanding if the input set contains many flexible ligands. PharmaGist is a free web server that can identify a consensus pharmacophore of a set of up to 32 ligands in a few minutes. Alternatively, structure-based approaches require a ligand-bound structure and identify a potential pharmacophore by analyzing the interaction site. ZINCPharmer provides a mechanism for deriving an initial pharmacophore hypothesis directly from structures within the PDB (Protein Data Bank), and also supports importing pharmacophore definitions developed using more computationally demanding approaches implemented in third-party tools.

Given a library of explicit compound conformations, conformers that match a 3D pharmacophore can be found using either fingerprint-based or alignment-based approaches. Fingerprints are well suited for similarity metrics, but, since they discretize the pharmacophore representation, provide inexact results. The EDULISS online database provides fingerprint-based screening of a single-conformer library of a few million compounds, but the query fingerprint must be manually constructed from pairwise distance constraints. Alignment-based approaches produce more accurate and interpretable results, at the expense of more computation. For example, a library of fewer than a million conformers may take minutes or hours to screen. However, since there are substantially fewer protein targets than there are possible ligands, alignment-based pharmacophore screening can be used effectively when performing a reverse screen that identifies matching protein targets instead of ligands. PharmMapper takes as input a single ligand and screens a database of over 7000 receptors for potential targets.

Both fingerprint and alignment-based approaches typically evaluate every conformer in the library, resulting in search times that scale with the size of the database. Newer methods, such as Pharmer and Recore use indexing approaches so that search times scale with the complexity and breadth of the query, not the size of the library. ZINCPharmer uses the open-source Pharmer software to enable the interactive search of more than 176 million conformations in just a few minutes, if not seconds.

WORKING:

ZINCPharmer searches a database of conformations calculated from the purchasable compounds of the ZINC database. ZINC is a comprehensive collection of commercially available, biologically relevant compounds suitable for screening. Purchasable compounds have an expected availability of <10 weeks and are either available from vendor stock or are make-on-demand. The ZINCPharmer library is synchronized with the ZINC library on a monthly basis. Compounds are both added and removed to maintain consistency and ensure that only currently purchasable compounds are retained. ZINC compounds are converted into 3D conformations using omega2 from OpenEye Scientific Software. Conformers are generated using the default settings and -rms.7, which improves the sampling of conformational space compared to the default setting of .5. The 10 best conformers are saved.

The generated conformers are converted into an efficient search format using the Pharmer open-source software. Pharmer identifies hydrophobic, hydrogen bond donor/acceptor, positive/negative ions and aromatic pharmacophore features using the SMARTS matching functionality of the OpenBabel toolkit. Currently, the default set of SMARTS definitions is used, but these are subject to refinement based on user input. These features are stored in an efficient spatial index to support the rapid search of large chemical libraries.

The graphical user interface for defining, refining and visualizing pharmacophore queries and their results is implemented using JavaScript and the Java-based Jmol molecular viewer. A modern, standards compliant browser with a recent Java plugin is required. Session state, which includes the pharmacophore definitions, can be saved in a human-readable JSON (JavaScript Object Notation) format and the aligned search results can be saved in the sdf molecular format. An internet forum hosts a user guide and provides technical support.

DEFINING A PHARMACOPHORE QUERY

Using the Pharmer software, ZINCPharmer can automatically extract a set of pharmacophore features from molecular structure. Each feature consists of the feature type (hydrophobic, hydrogen bond donor/acceptor, positive/negative ion or aromatic), a position, and a search radius. Features may be derived from a single ligand structure, a protein–ligand structure, a protein–protein structure or from the output of third-party software.

REFINING A QUERY

Although ZINCPharmer is capable of automatically extracting a pharmacophore from an interaction, it is expected that the user will further refine the query to enhance its specificity and applicability. This can be done by editing the properties of the query or by applying filters to the results.

PHARMACOPHORE SEARCH

Having defined a pharmacophore, searching for matching purchasable compounds is as simple as clicking the ‘Submit Query’ button. Searches take anywhere from a few seconds to a few minutes. Queries with more features, queries with many hydrophobic features (which are the most common features), queries with large search tolerances and symmetric queries (which require the processing of many orientations per a matching conformer) will have longer search times. Results are returned and displayed in the results browser as they are found. An orientation of a conformer is only returned as a hit if all the matching features are within the specified search tolerances of the query when the conformer is aligned to minimize the weighted RMSD.

RESULTS VISUALIZATION

Each hit represents a unique orientation of a conformation to the query. For each hit, the ZINC identifier, RMSD to the query, molecular weight (‘Mass’), and number of rotatable bonds (‘RBnds’) is shown. The ZINC identifier is a hyperlink that points to the corresponding compound web page in the ZINC database where purchasing information may be found. The results may be sorted by any of the numerical properties by clicking on the property heading in the results table. The complete set of oriented hits may be saved to an sdf file through the ‘Save Results’ button. The hits in this file are unordered and include the RMSD to the query as extra data attached to each molecule. This file is immediately useful as input to a secondary screening protocol such as ranking by energy minimization.

Individual hits are visualized with the query and a receptor (if present) by clicking on the corresponding row in the results browser. The viewer tab contains a wide assortment of colors and styles (wireframe, stick, spheres, etc.) for visualizing the results, the query ligand, the receptor residues and the receptor surface.

Different ways to view the receptor, ligand and result in the viewer panel:

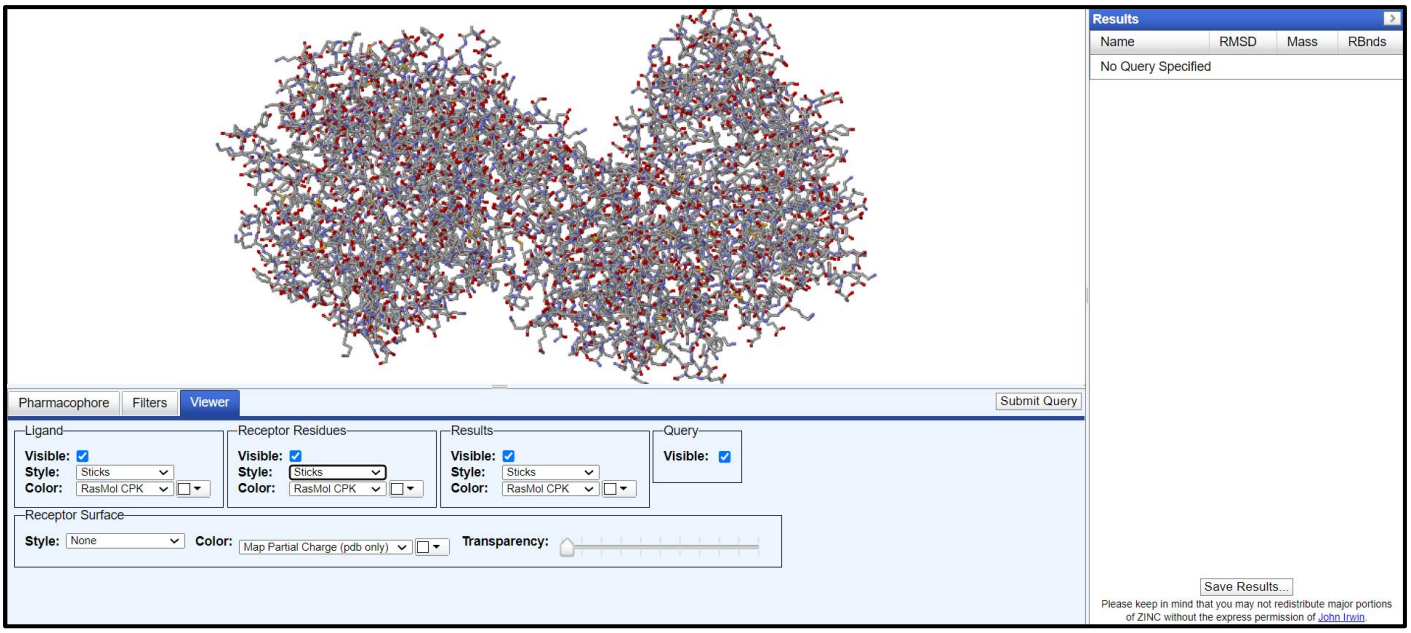

FIG 1. Visualisation in sticks style

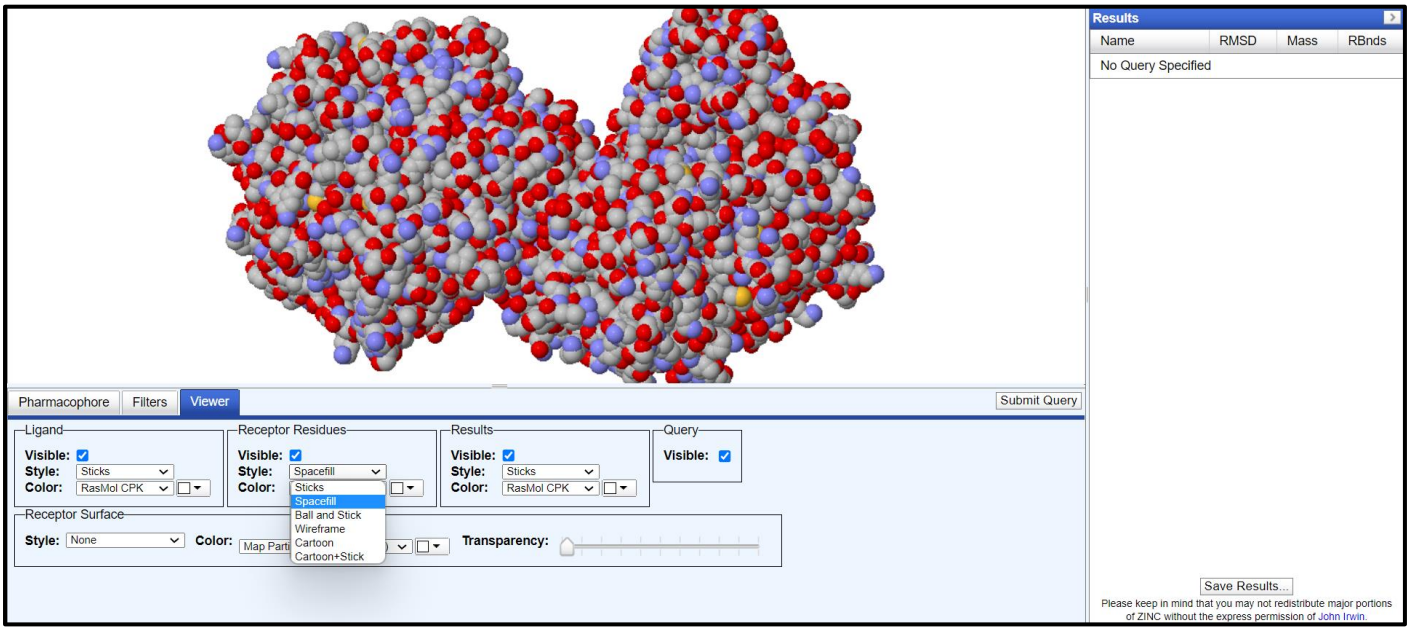

FIG 2. Visualisation in spacefill style

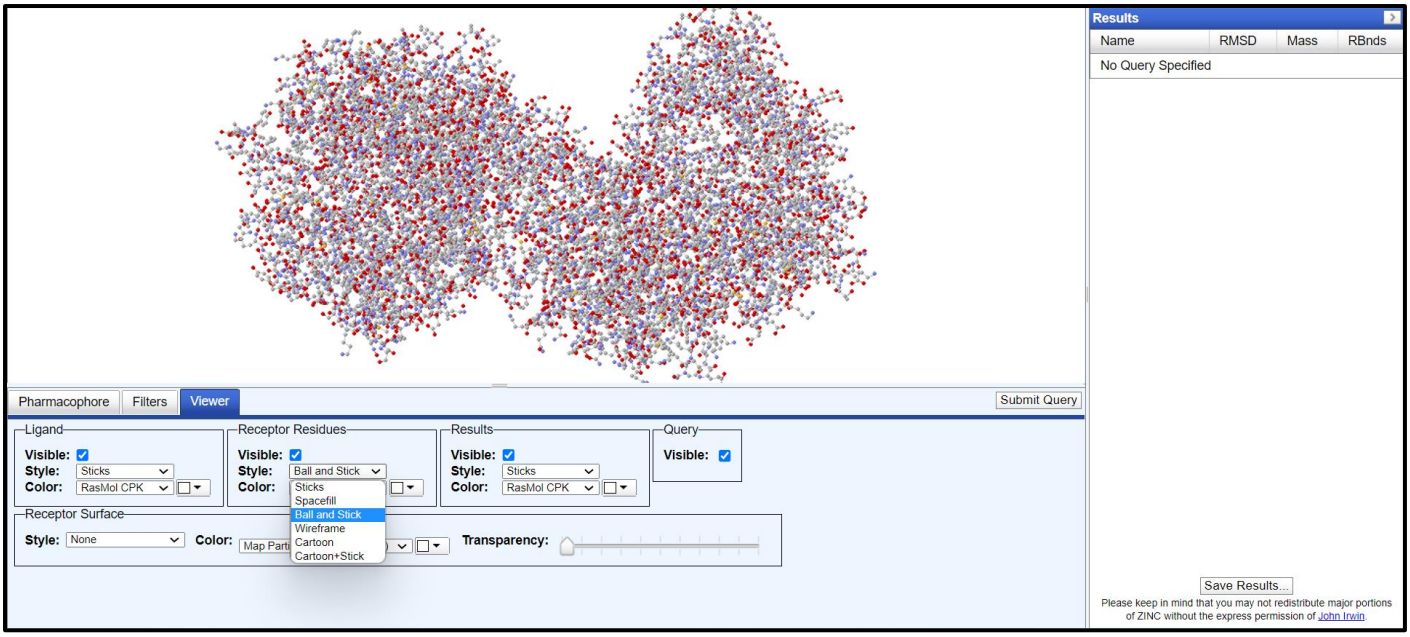

FIG 3. Visualisation in Ball and Stick style

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DATE: 08/10/2022

WEBLEM 5a

PharmMapper

(URL: http://www.lilab-ecust.cn/pharmmapper/)

AIM:

To generate and analyze Pharmacophore map for query Ampicillin (PubChem id: 6249) using PharmMapper web server.

INTRODUCTION:

Ampicillin is a semisynthetic penicillin derivative. A beta-lactam antibiotic, ampicillin is active against gram-positive cocci, including nonpenicillin resistant streptococcal, staphylococcal, and enterococcal species. It displays activity against some gram-negative organisms, gram-positive anaerobic organisms, and gram-negative anaerobic organisms. Ampicillin also has activity against certain spirochetes. Sulbactam, a beta-lactamase inhibitor, is administered with ampicillin to extend its spectrum of activity against penicillinase producing bacteria. Ampicillin is used for the treatment of upper and lower respiratory infections, skin and skin structure infections, urinary tract infections, and otitis media.

PharmMapper Server is a freely accessed web-server designed to identify potential target candidates for the given probe small molecules (drugs, natural products, or other newly discovered compounds with binding targets unidentified) using pharmacophore mapping approach. Benefited from the highly efficient and robust mapping method, PharmMapper bears high throughput ability and can identify the potential target candidates from the database within a few hours.

PharmMapper is backed up by a large, in-house repertoire of pharmacophore database extracted from all the targets in TargetBank, DrugBank, BindingDB and PDTD. Over 7,000 receptor-based pharmacophore models (covering 1,627 drug targets information, 459 of which are human protein targets) are stored and accessed by PharmMapper. PharmMapper finds the best mapping poses of the user uploaded molecules (in Tripos Mol2 or MDL SDF format) against all the targets in PharmTargetDB and top N potential drug targets as well as respective molecule's aligned poses are outputted.

METHODOLOGY:

- Retrieve 2D structure of Ampicillin in .sdf format from Pubchem database (URL: https://pubchem.ncbi.nlm.nih.gov/)
- Open homepage of PharmMapper. (URL: http://www.lilab-ecust.cn/pharmmapper/)
- Go to the submit job tab.
- Submit the Ampicillin structure retrieved from Pubchem database.
- Copy the job id and paste in the get result tab.
- Observe and interpret the results.

OBSERVTIONS:

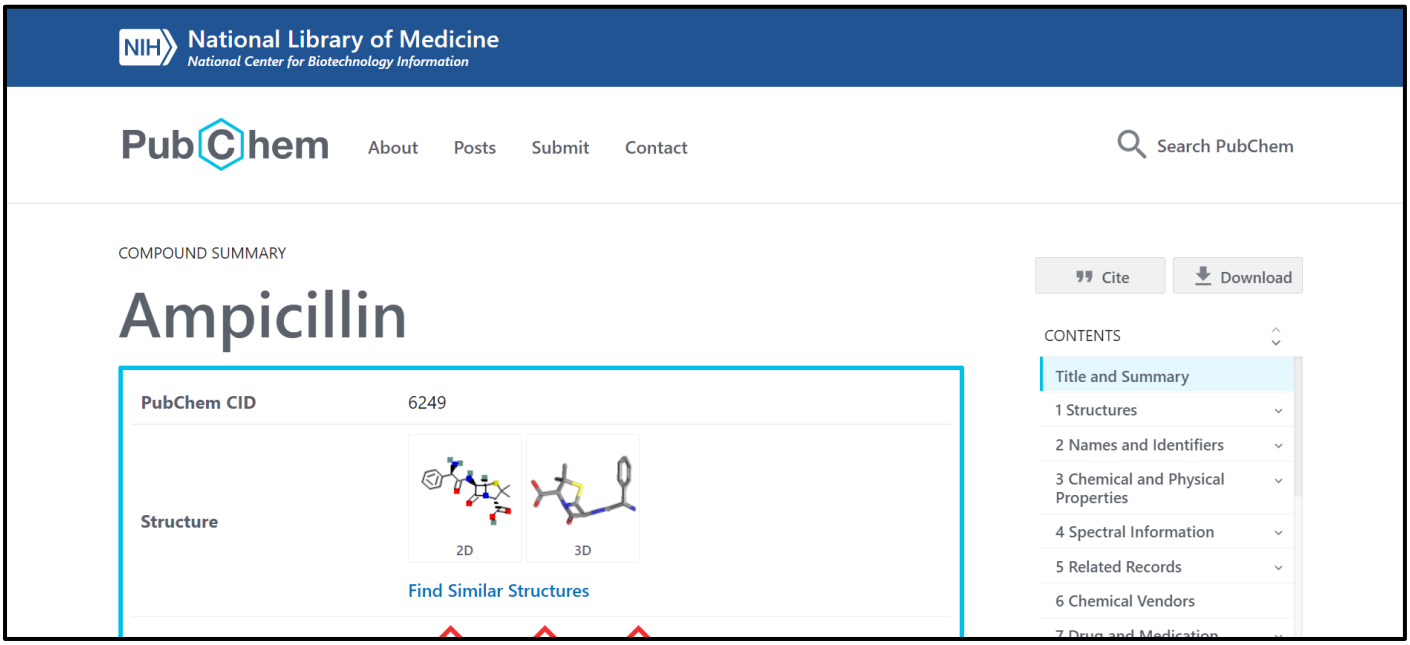

Fig1. Pubchem database page for Ampicillin

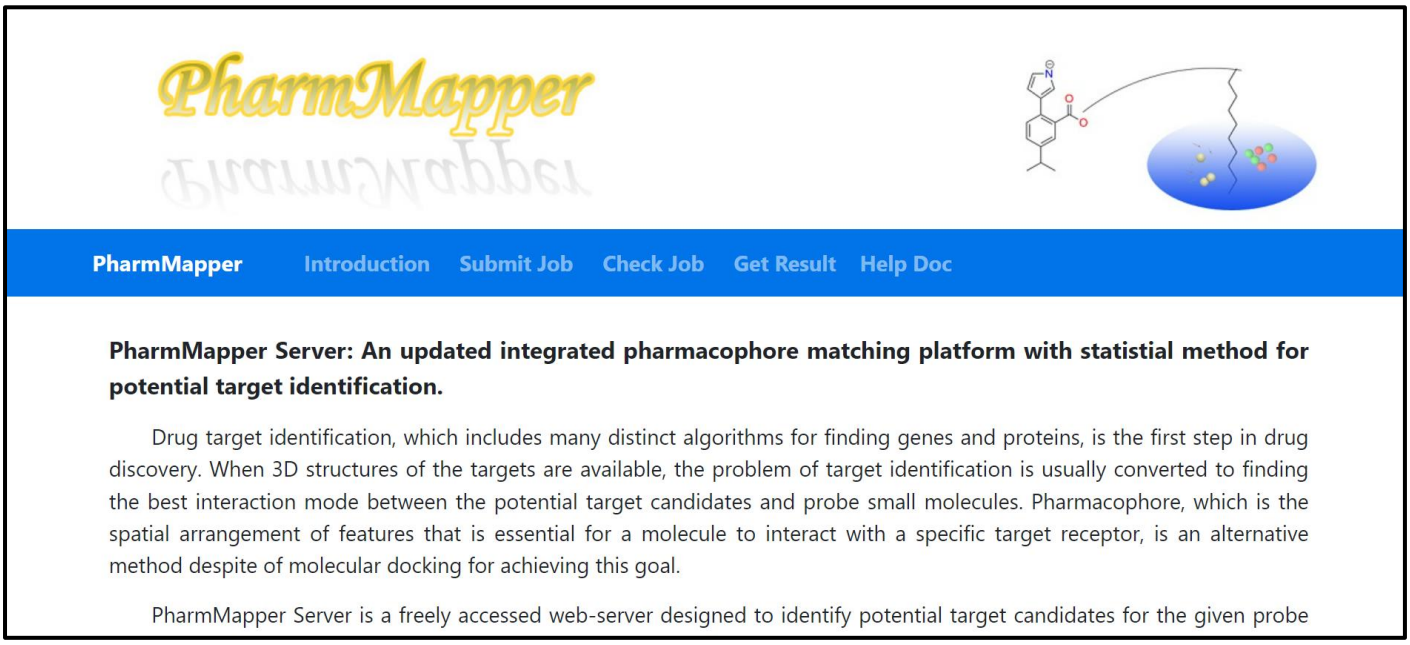

FIG 2. Homepage of PharmMapper server

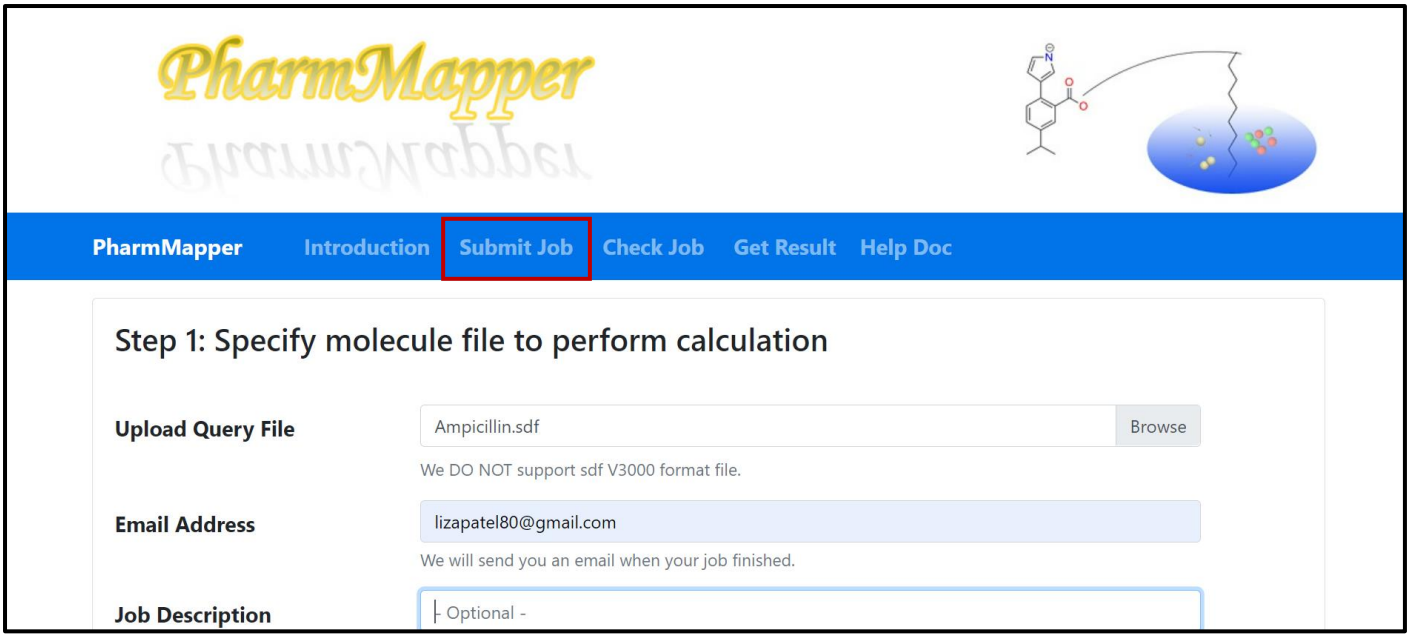

FIG 3. Submission of Ampillicin structure on server

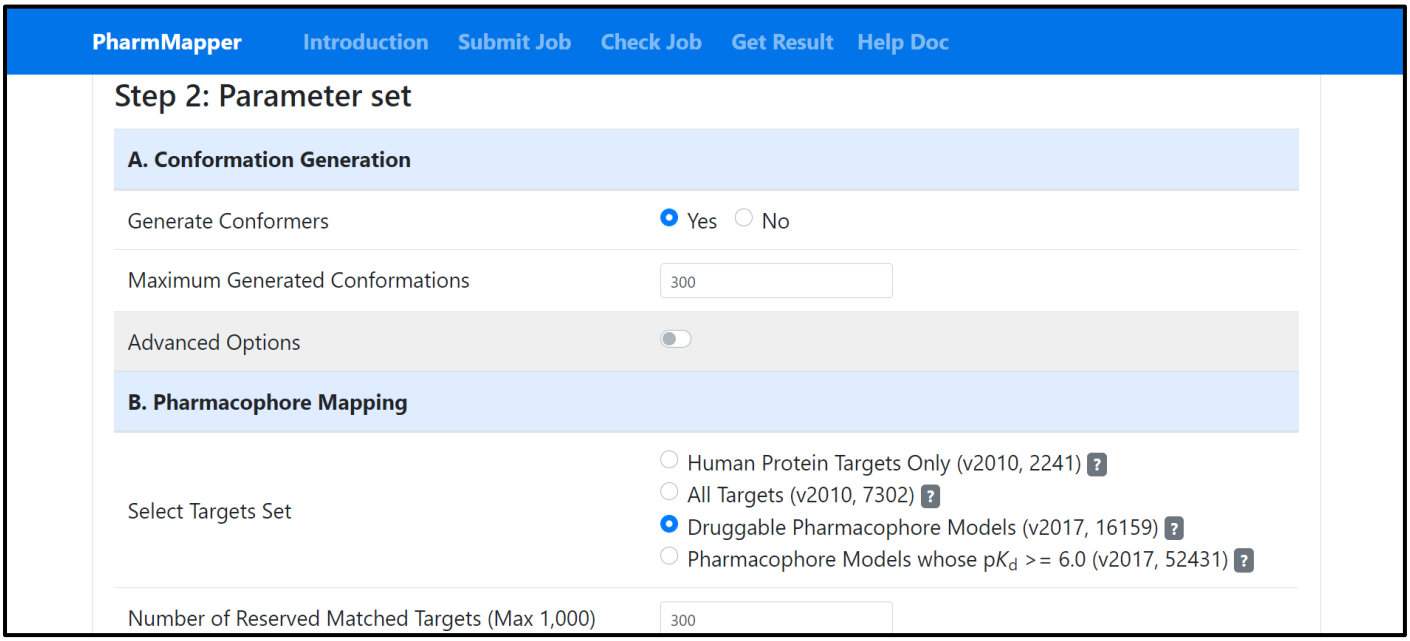

FIG 4. Parameters for the query submission

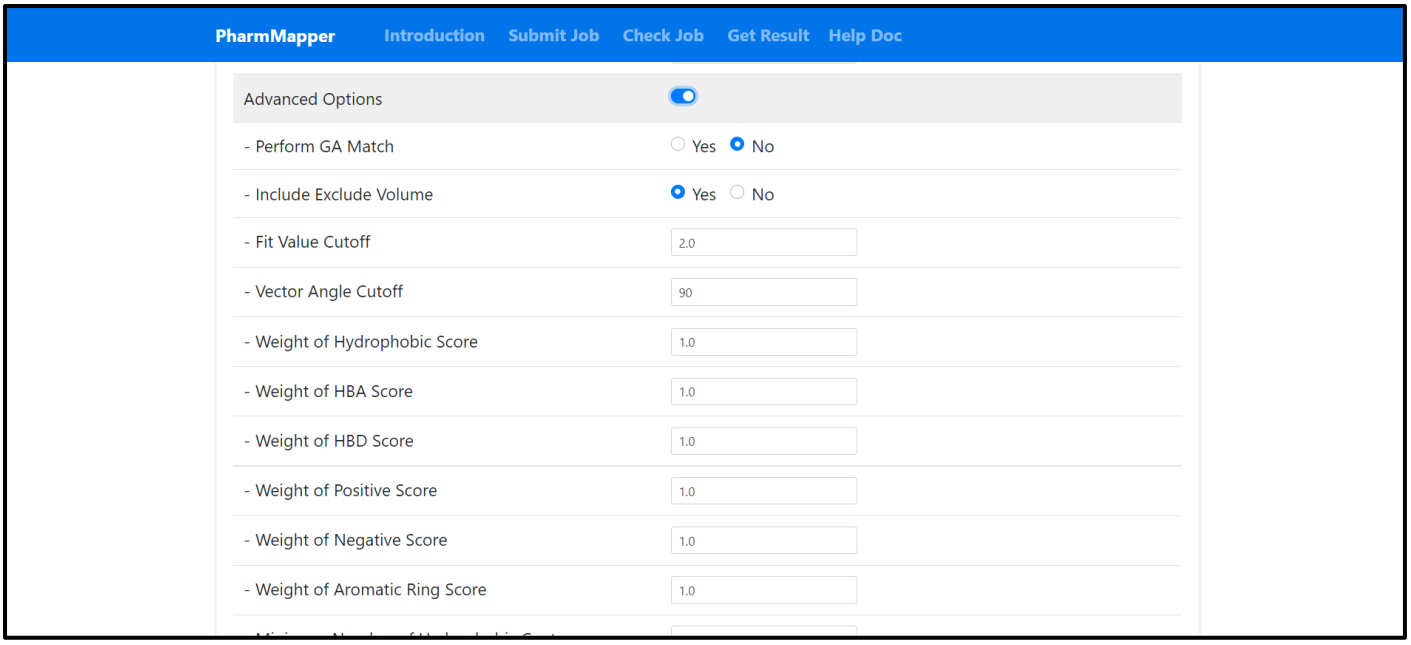

FIG 5. Advanced options to set parameters

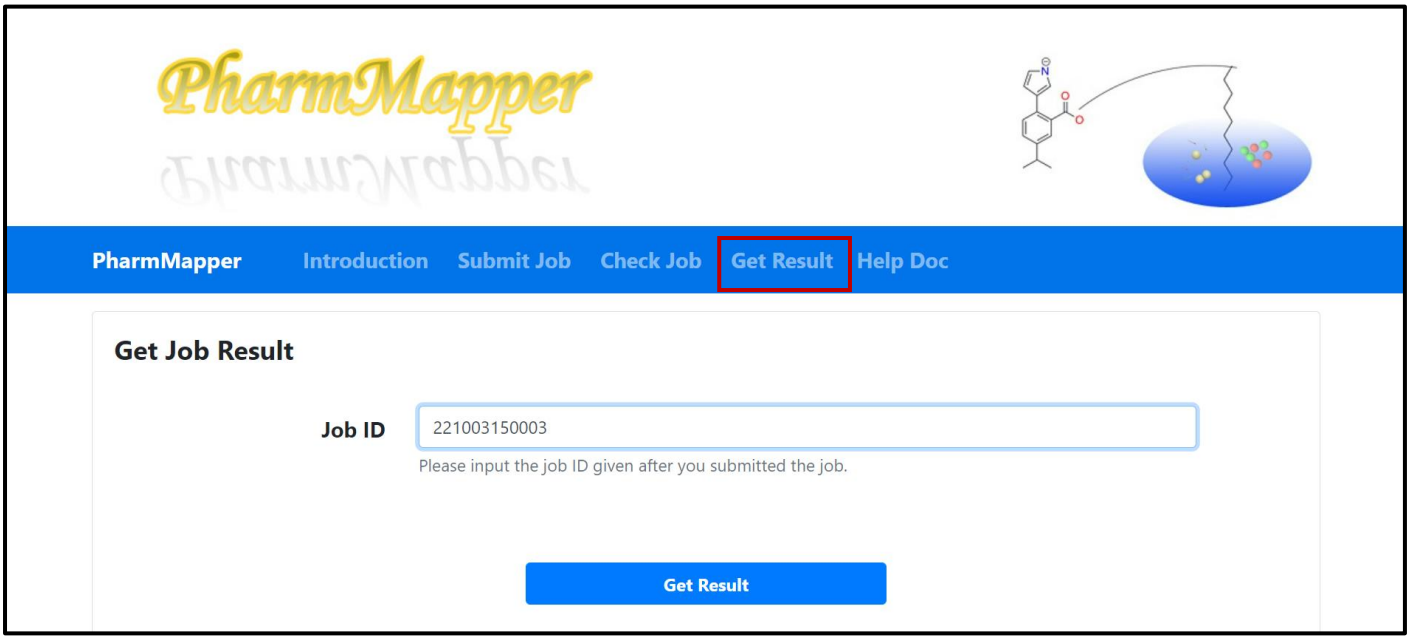

FIG 6. Submission of job ID to get the results

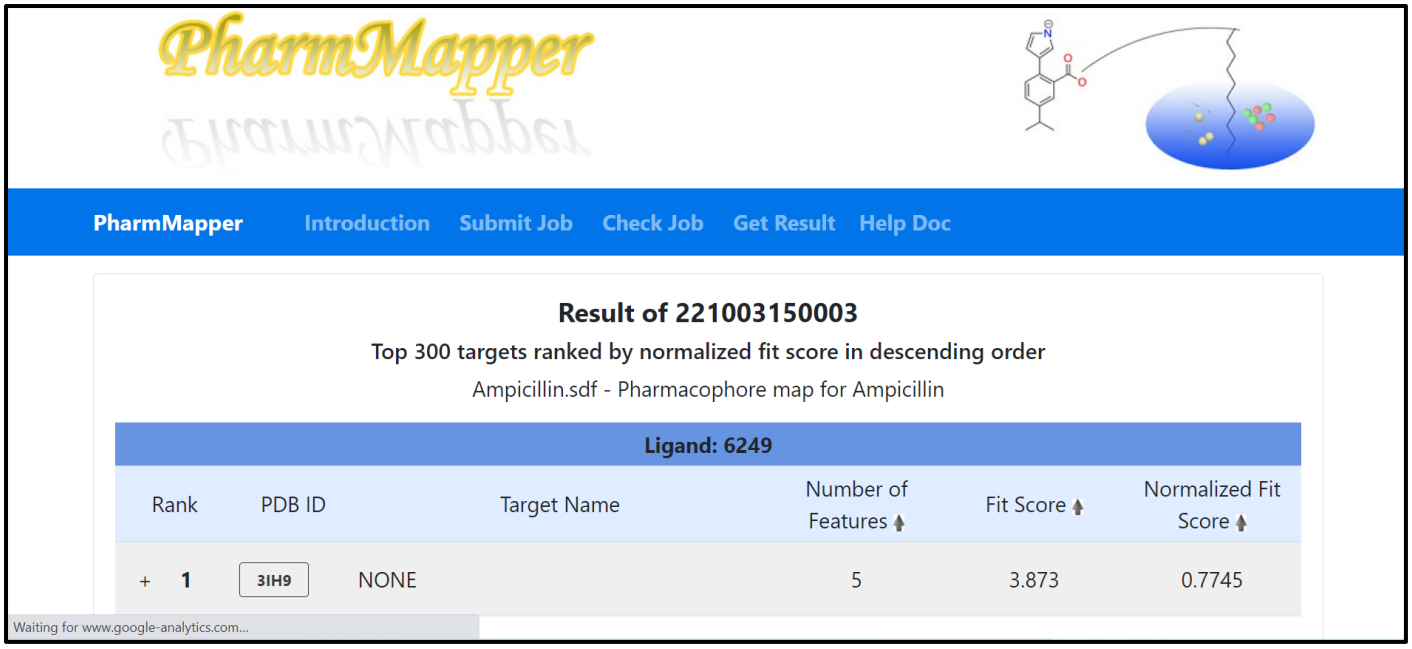

FIG 7. Targets obtained for the query hit

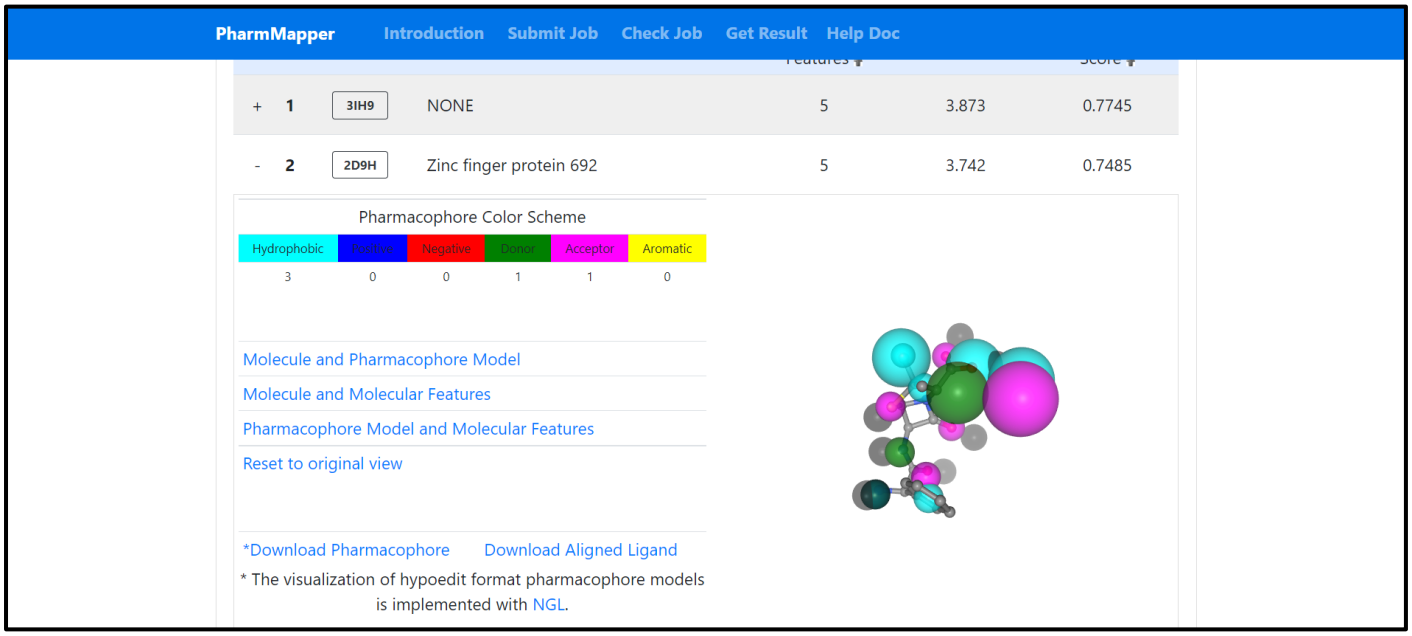

FIG 8. Result for Zinc finger protein 692 protein target

RESULTS:

To generate and analyze Pharmacophore map for query Ampicillin (PubChem id: 6249) PharmMapper web server was used. 300 targets ranked with normalized fit score in descending order were retrieved. Molecule and pharmacophore model was observed for Zinc finger protein 962 with fit score of 3.742 and 5 matching features with query was observed.

CONCLUSION:

PharmMapper Server can be used identify potential target candidates for the given probe small molecules (drugs, natural products, or other newly discovered compounds with binding targets unidentified) using pharmacophore mapping approach. Benefited from the highly efficient and robust mapping method, PharmMapper bears high throughput ability and can identify the potential target candidates from the database within a few hours.

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DATE: 08/10/2022

WEBLEM 5b

ZINCPharmer

(URL: http://zincpharmer.csb.pitt.edu/)

AIM:

To perform virtual screening based on pharmacophore features for Dactinomycin (PubChem Id- 457193) using ZincPharmar web server.

INTRODUCTION:

Dactinomycin is used in combination with other medications, surgery, and/or radiation therapy to treat Wilms' tumor (a type of kidney cancer that occurs in children) and rhabdomyosarcoma (cancer that forms in muscles) in children. Dactinomycin is also used in combination with other medications to treat certain types of testicular cancer and Ewing's sarcoma (a type of cancer in bones or muscles). Dactinomycin is also used alone or in combination with other medications to treat gestational trophoblastic tumors (a type of tumor that forms inside a woman's uterus while she is pregnant). Dactinomycin may also be used to treat certain types of cancerous tumors that are located in a specific area of the body. Dactinomycin is a type of antibiotic that is only used in cancer chemotherapy. It works by slowing or stopping the growth of cancer cells in your body.

ZINCPharmer is free pharmacophore search software for screening the purchasable subset of the ZINC database (updates occur monthly). ZINCPharmer can import LigandScout and MOE pharmacophore definitions, as well as identify pharmacophore features directly from structure.

METHODOLOGY:

- Retrieve structure of protein 6VSB from PDB database in .pdb format (URL: https://www.rcsb.org/)
- Retrieve 2D of Dactinomyin in .sdf format from Pubchem database (URL: https://pubchem.ncbi.nlm.nih.gov/)
- Open homepage of ZINCPharmer. (URL: http://zincpharmer.csb.pitt.edu/)
- Click on “Search ZINC”
- Load the receptor i.e the protein structure.
- Load the features i.e the Dactinomycin structure
- Enable the features and apply filters
- Click on “Submit Query”
- Observe and interpret the results.

OBSERVATIONS:

FIG 1. Structure of 6VSB protein from PDB database

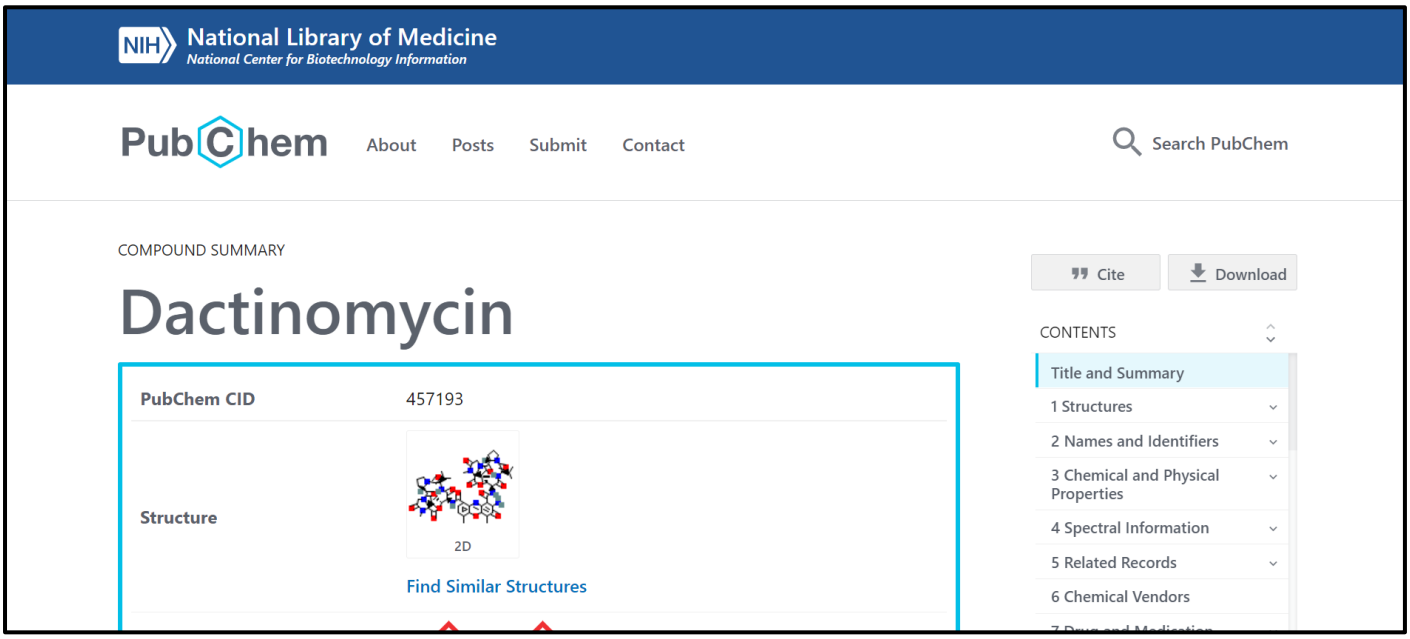

FIG 2. Structure of Dactinomycin from PubChem database

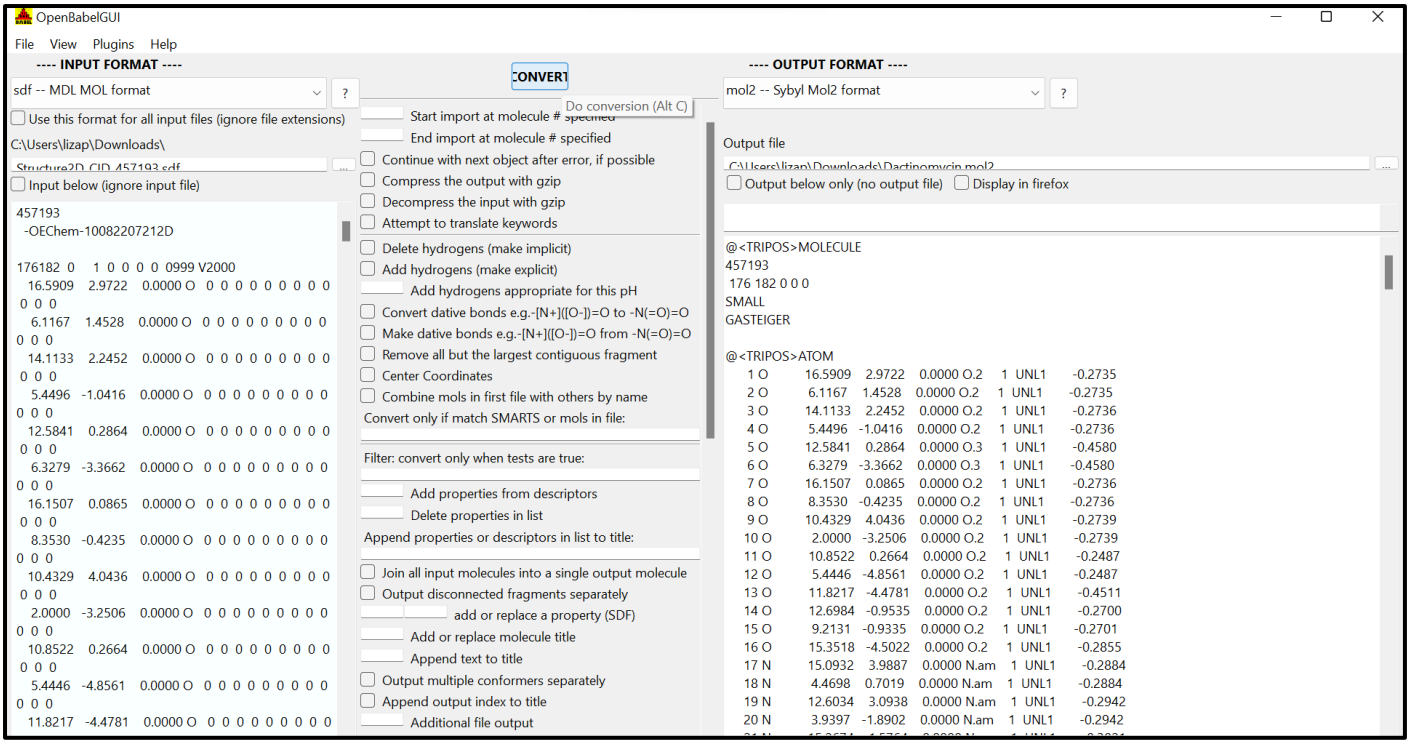

FIG 3. Conversion of Dactinomycin structure from .sdf file format to .mol2 file format using open babel tool

FIG 4. Homepage of ZINCPharmer server

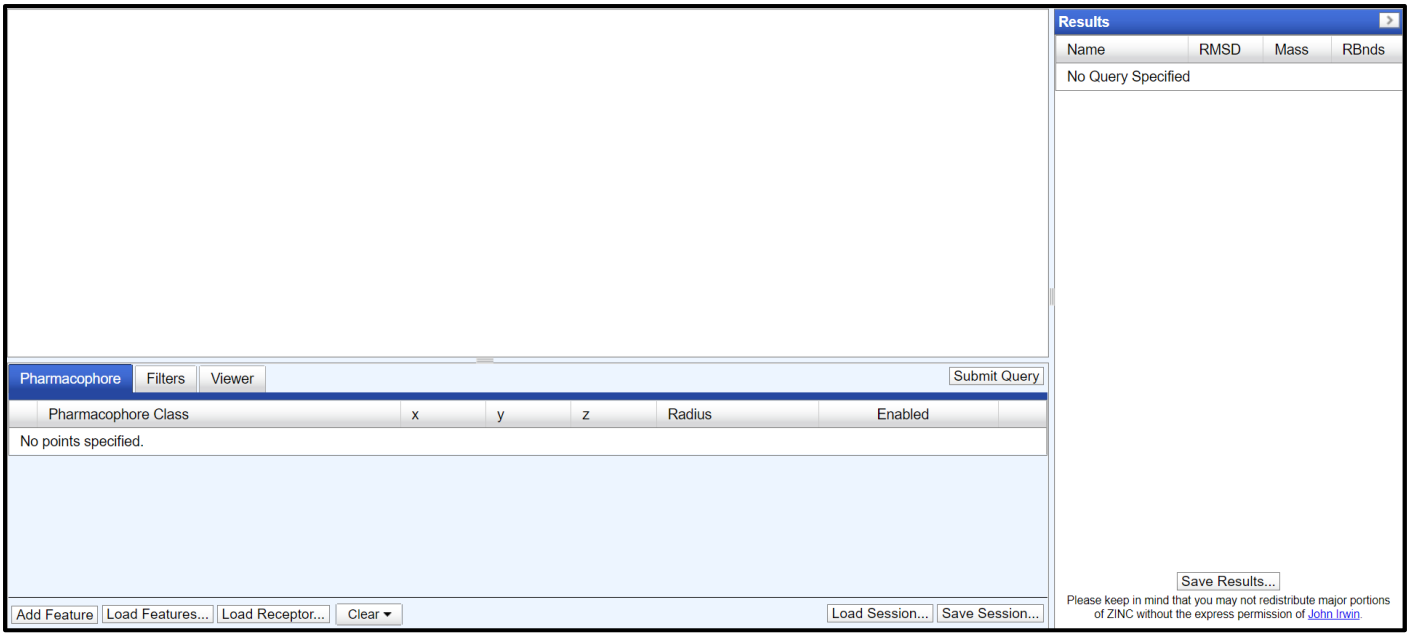

FIG 5. Panel for ZINC Search

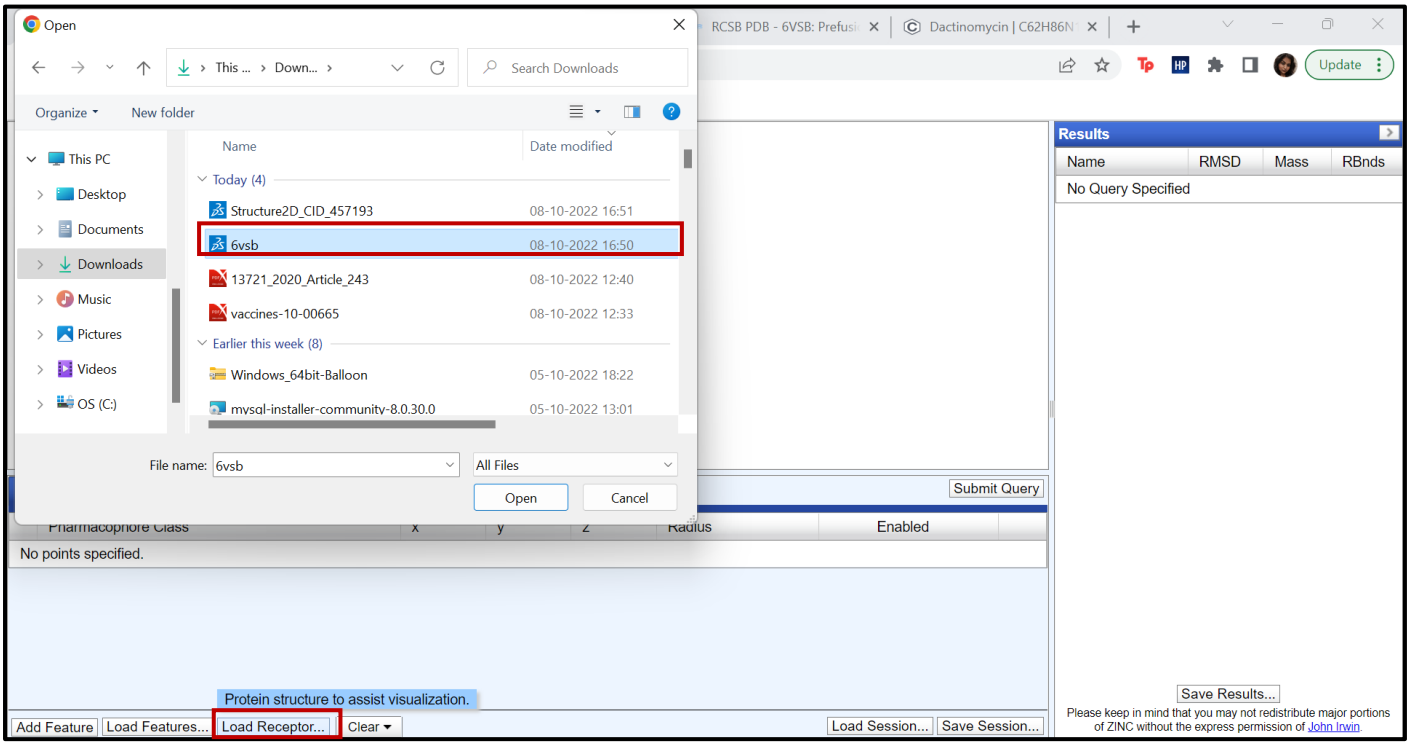

FIG 6. Loading receptor

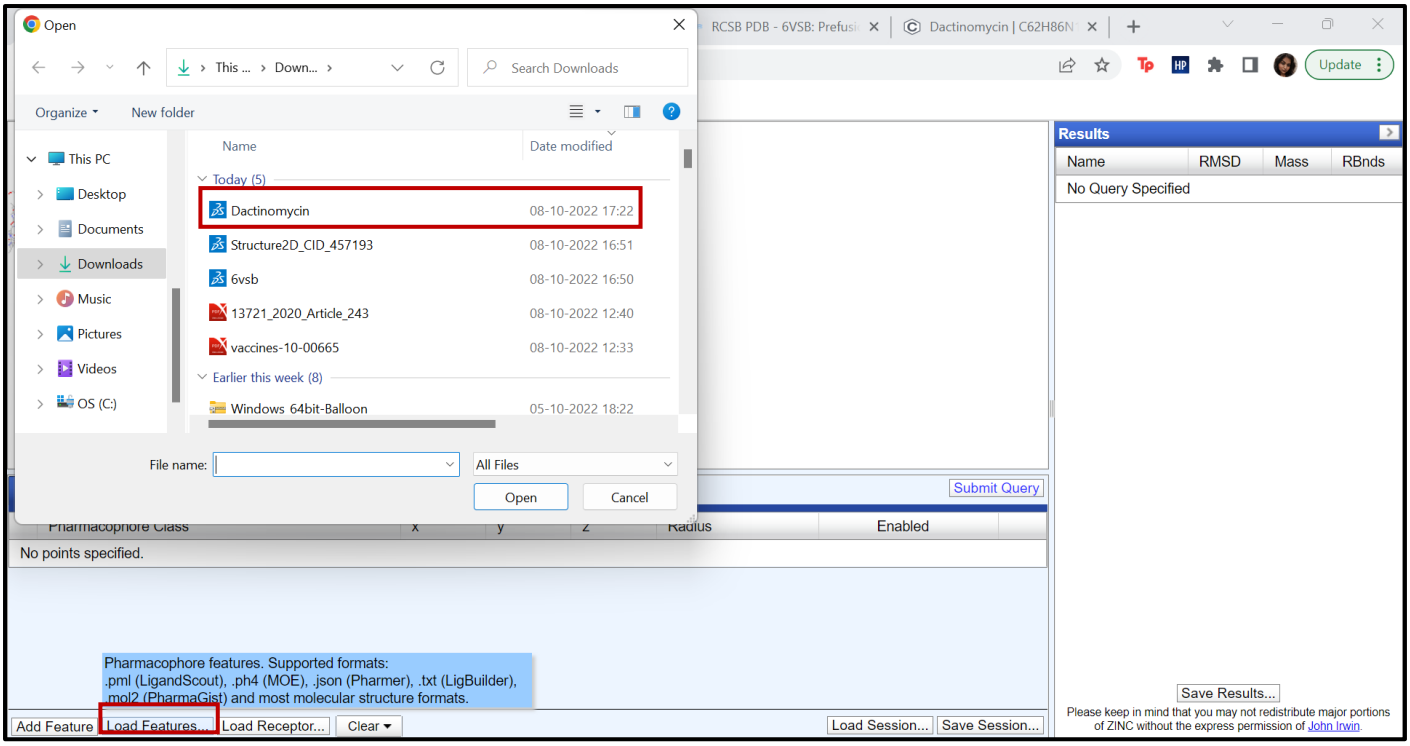

FIG 7. Loading features for query

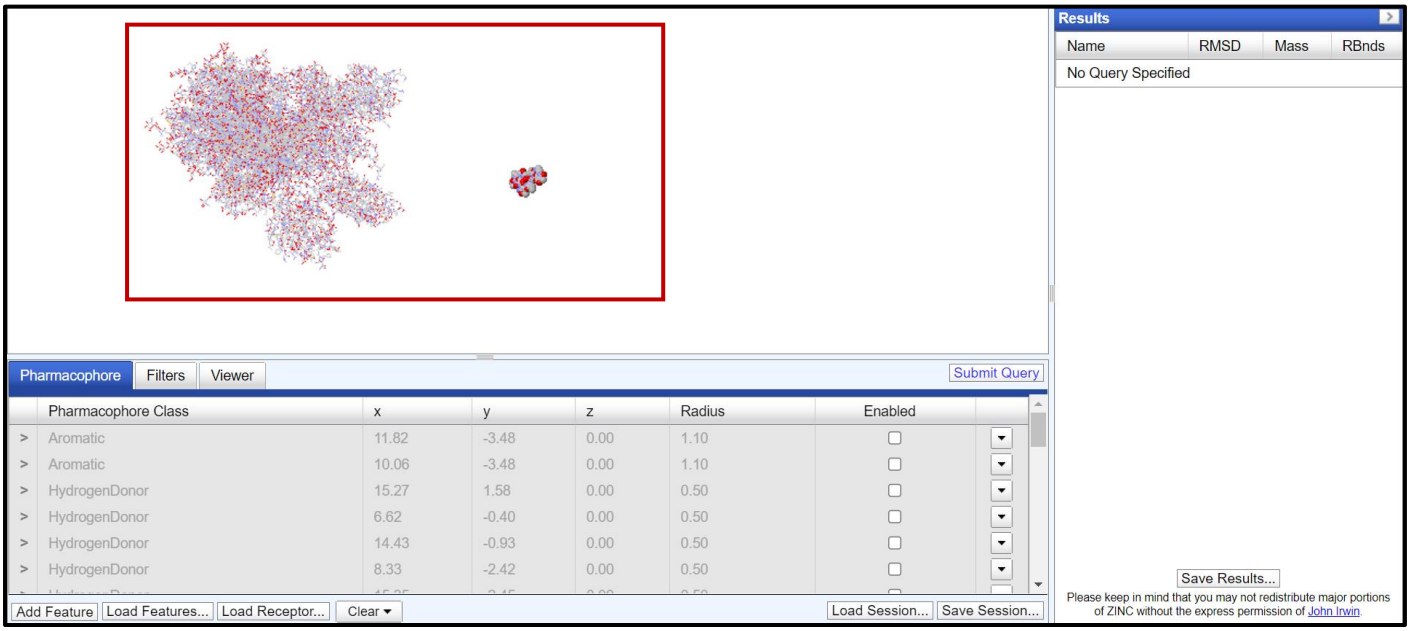

FIG 8. Loaded receptor and features for analysis

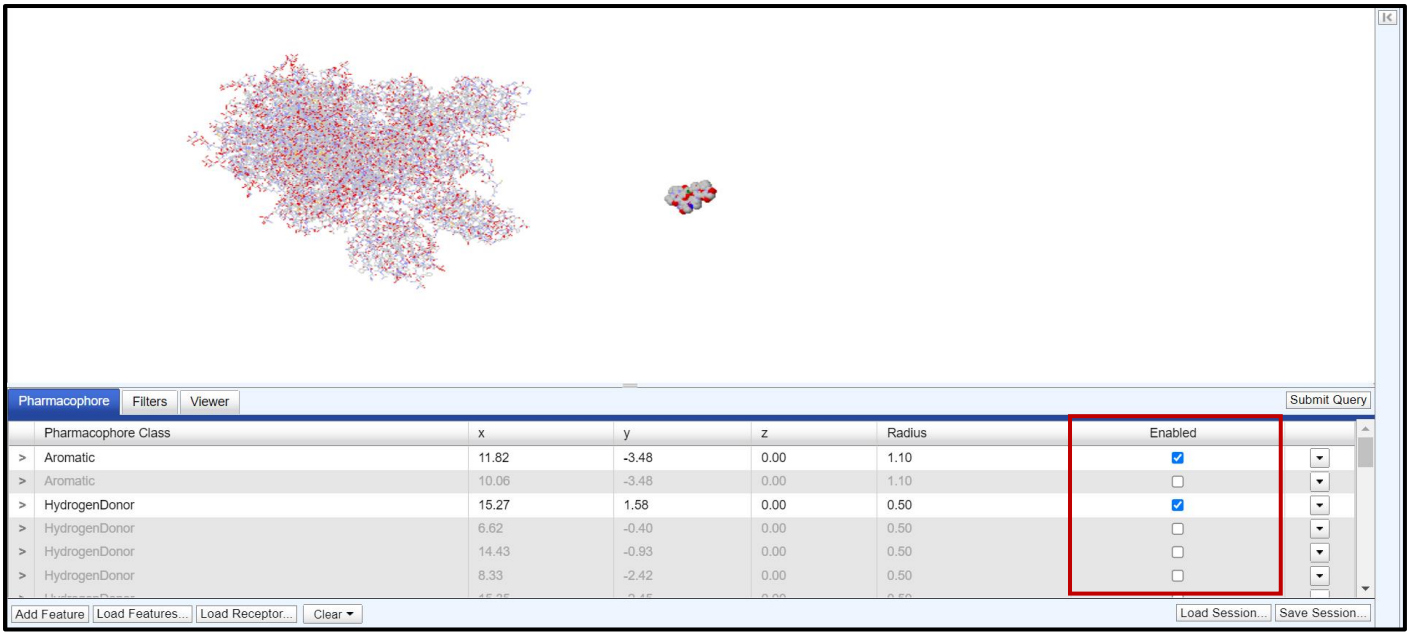

FIG 9. Enabling features for the search

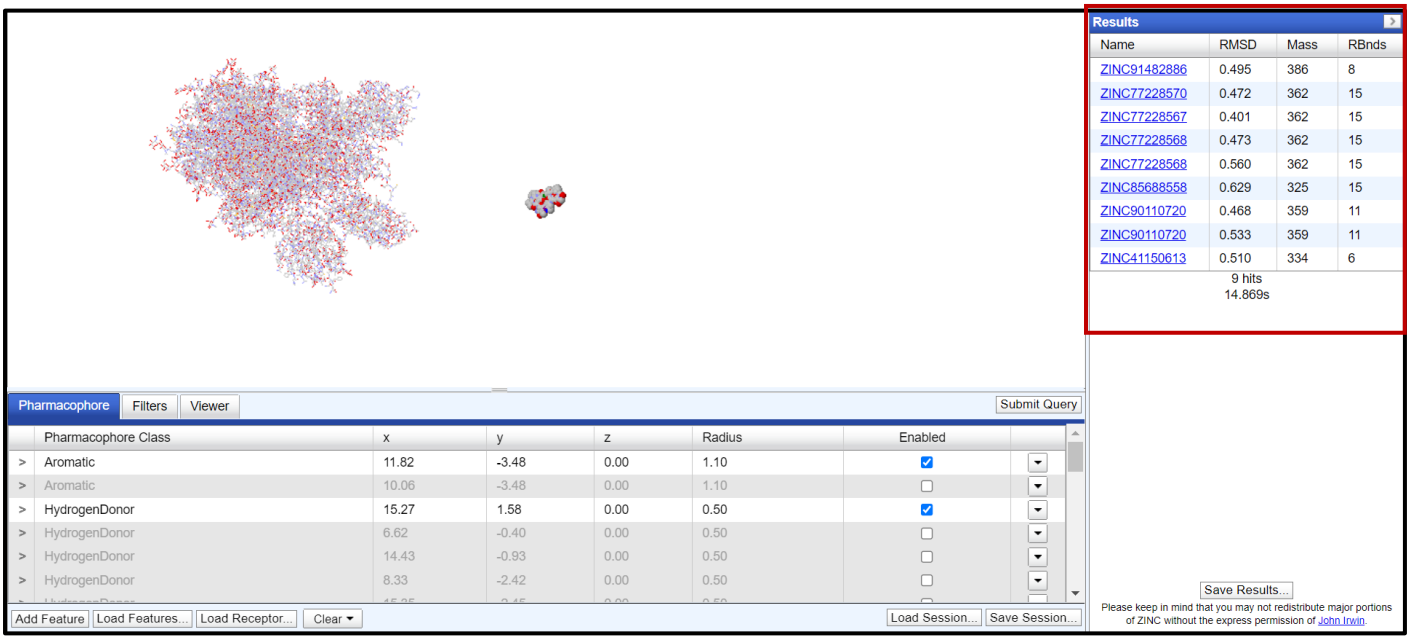

FIG 10. Search results

FIG 11. Applying filters to refine the search

FIG 12. Search results after refinement

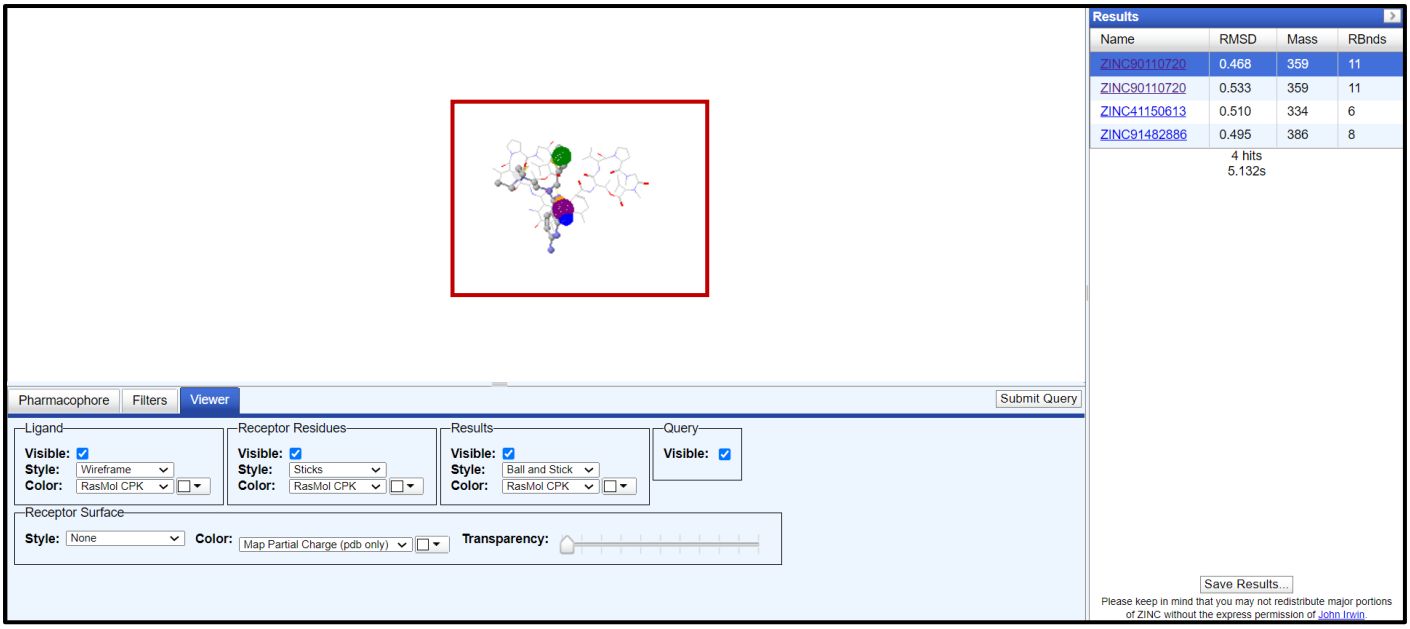

FIG 13. ZINC conformer mapped over ligand "Dactinomycin"

RESULTS:

Virtual screening based on pharmacophore features for Dactinomycin (PubChem Id- 457193) was performed using ZincPharmar web server. After submitting the query 9 hits were obtained and after applying filters for molecular weight and rotatable bonds 4 hits were obtained based on provided pharmacophore features.

CONCLUSION:

A pharmacophore describes the structural arrangement of the essential molecular features of an interaction between a ligand and its receptor. Searching chemical libraries for compounds that match a specific pharmacophore is an established method of virtual screening. The two main challenges of pharmacophore-based virtual screening are identifying a representative pharmacophore for an interaction and then identifying the compounds within a relevant chemical library that match the pharmacophore. ZINCPharmer is a pharmacophore search engine for purchasable chemical space that addresses both these challenges. The ultimate goal here is the discovery of novel compounds which exhibit a set of desired pharmacophoric features that are considered crucial for biological activity towards a particular target of interest. Hit-lists made up of molecules belonging to different structural classes can serve as a valuable source of "ideas" for the development and optimization of novel lead compounds that might not have been discovered by a traditional rational drug design processes alone.

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